Hepatic intra-arterial and systemic chemotherapy followed by maintenance therapy for the treatment of cholangiocarcinoma

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Aim: The aim is to report clinical outcomes of hepatic intra-arterial (IACT) and systemic chemotherapy (SCT), followed by gemcitabine-based maintenance therapy (maintenance), for the treatment of relapsed or unresectable cholangiocarcinoma. **Patients & methods:** In this retrospective observational study, 145 cholangiocarcinoma patients were treated with Epirubicin-Cisplatin as IACT associated with Capecitabine or 5-fluorouracil as SCT. Maintenance was performed with gemcitabine-based schedule. Toxicity was assessed with NCI-CTCAE and tumor response with RECIST 1.1. **Results:** Tumor response was complete in 1%, partial in 20%, stable disease in 48% and progression in 31% of patients (3 months after therapy). The most frequent adverse events were: anemia (24%), nausea and vomiting (33%), alopecia (60%). **Conclusion:** Cholangiocarcinoma patients may benefit from IACT-SCT. Maintenance may prolong clinical benefits. ClinicalTrials.gov registry Identifier: NCT01920503.

First draft submitted: 23 Jan 2017; Accepted for publication: 3 August 2017; Published online: 31 August 2017

Carcinoma of the biliary tract can be classified according to tumor location as intrahepatic or extrahepatic cholangiocarcinoma (CCA). Biliary tract has a poor prognosis (5-year survival <5%) [1]. CCA, after hepatocellular carcinoma, is the most frequent liver primary cancer accounting for 5–10% of liver malignancies [2]. Cholangiocarcinoma first line treatment is surgery, however, it is not possible for at least 75% of the patients. This is due to the advanced stage of disease at diagnosis [3]. The median survival for unresectable cholangiocarcinoma patients is 5–8 months [4,5]. Unresectable intrahepatic cholangiocarcinoma (ICCA) and extrahepatic biliary cancer (ECCA) have a modest benefit from current systemic therapies. Systemic chemotherapy (SCT) using gemcitabine in combination with cisplatin or biologics results in an overall survival (OS) of about 1 year [6]. The 5-fluorouracil (5-FU) is widely adopted as single drug for cholangiocarcinoma. Its efficacy is low with response rates (RR) ranging from 10 to 20% [7]. ICCA seems to have a slight longer survival in respect to ECCA [1,2,5].

Intrahepatic cancers are often unresectable and confined to the liver. Extrahepatic cancers are frequently not confined to the liver, but they receive blood support from the common hepatic artery. For this reason, the regional therapy through hepatic artery (intra-arterial chemotherapy

KEYWORDS

- biliary tract cancer
- cholangiocarcinoma
- intra-arterial chemotherapy
- tumor response

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[IACHT]) was selected as first line treatment in the present study. This was done in order to obtain high drug concentrations in the target disease. IACHT was associated to SCHAT [8,9].

The combinations of cytotoxic drugs such as the ECF and ECX schedules are used in other studies. Both protocols include epirubicin and cisplatin via IACHT in association with systemic infusion of 5-FU (ECF) or oral capecitabine (ECX) [8,9]. This protocol offers greater benefits than 5-FU alone resulting in 31.5% of RR and 11.6 months of median progression-free survival [8,9].

It is not known how long the treatment for cholangiocarcinoma patients should be performed. For this reason the CHT is prolonged for patients obtaining complete response (CR) or partial response (PR) after first line treatment. These patients receive a maintenance therapy with noncross-resistant gemcitabine-based schedule. Maintenance therapy is used in several tumors: hematologic malignancies, advanced non-small-cell lung cancer, urothelial carcinoma and cholangiocarcinoma [10–13]. This method shows good tumor response, improvement of survival and progression delay.

The purpose of maintenance chemotherapy is to prolong the clinical benefit attained with the first line therapy. It can be done using the same drug of the previous treatment. Another method consists of switching to a new and potentially noncross-resistant agent (sequential therapy). The purposes of maintenance therapy are efficacy increment, resistance reduction, tumor response maximization, survival improvement and progression delay (Table 1) [14–16]. Gemcitabine-based schedule is commonly used for the treatment of cholangiocarcinoma. It is also used in second line chemotherapy with significant tumor response [17–19]. For this reason it is used for the maintenance method.

This retrospective observational cohort study reports the results of the combined therapy IACHT-SCHAT on 145 patients with unresectable or recurrent ICCA and ECCA. It also presents the results of maintenance therapy applied on patients positively responding to IACHT-SCHAT. The purpose of this study is to report clinical outcomes of IACHT-SCHAT and maintenance therapy for the treatment of cholangiocarcinoma.

Methods

• Ethics

The study was reviewed and approved by Institutional Review Board. All enrolled patients

signed informed written consent prior to study enrollment as requested by local Institutional Review Board. This report is part of the study registered in clinicaltrials.gov registry (Identifier: NCT01920503).

• Patients

This was a retrospective cohort study on clinical outcomes of patient tailored therapies used for the treatment of cholangiocarcinoma from January 2000 to June 2016 in three Italian Hospitals. A total of 145 consecutive patients with unresectable or relapsed cholangiocarcinoma were referred and received IACHT combined with SCHAT. These patients were not surgical candidates because of advanced tumor stage, relapsed tumors, comorbidities, refused the resection or elderly. A maintenance therapy was administered to patients reporting response to IACHT-SCHAT.

Patients were enrolled in the study if they fulfilled the following inclusion criteria: >18 years, histologically confirmed diagnosis of nonresectable cholangiocarcinoma; any type of systemic or locoregional therapy for cholangiocarcinoma before received, Eastern Cooperative Oncology Group performance status (ECOG) 0–2; tumor size evaluable according to RECIST version 1.1 [11]; and liver and renal function and hematological values compatible with chemotherapy; life expectancy ≥3 months.

Patients were excluded from the data collection if: contraindicated to angiographic and selective visceral catheterization; presence of large hepatic disease >50% of total liver, peritoneal carcinomatosis with ascites, lung metastases, abdominal lymph nodes metastases >5 cm; inflammatory intestinal disease; active infection; peripheral neuropathy ≥grade 2; pregnancy or breast feeding; other severe clinical impairment.

Data collected at baseline visit included demographics, extrahepatic metastases, previous therapies, disease staging and tumor dimension by CT scan and/or MRI, tumor marker levels. Patients, who had CR or PR after IACHT-SCHAT, received maintenance CHT in order to prolong the clinical benefit.

• Intra-arterial associated to intravenous chemotherapy

IACHT, administered through hepatic artery bolus, was performed using an angiographic catheter that was inserted in the femoral artery with the Seldinger method, and was repeated

Table 1. Reason for maintenance chemotherapy in cholangiocarcinoma.

Rationale	Motivation	Ref.
Efficacy increment	Only 25% of patients with advanced CCA receive second line chemotherapy after progression. The use of a maintenance chemotherapy will allow the treatment of >90% of indicated patients with the anticipated therapy	[12]
Resistance reduction	Resistance is due to the accumulation of spontaneous mutations, for this reason its onset with time (Goldie and Coldman hypothesis). The use of maintenance noncross-resistant chemotherapies could reduce the number of tumor cells and decrease the risk of resistance onset	[13]
Tumor response maximization	The use of maintenance chemotherapy with a sequential, noncross-resistant schedule may allow to maximize the tumor response, allowing the elimination of slower growing resistant cells (Norton–Simon hypothesis) that do not respond to first line chemotherapy	[14,15]
Survival improvement and progression delay	Maintenance with gemcitabine improves survival rates and the time to first progression of patients affected by urotelial carcinoma, who were previously treated with first line chemotherapy. Gemcitabine is efficacious also for the treatment of CCA. For this reason survival improvement and progression delay may be achieved also in CCA applying maintenance gemcitabine-based therapy after first line treatment	[10,16, 17]

CCA: Cholangiocarcinoma.

every 3 weeks [8,9]. The advantages of this therapy were the reduction of potential systemic adverse events: bone marrow toxicity, alopecia, vomiting and the increased efficacy of cytotoxic drugs in the liver, due to elevated first pass effect [7–10,20]. In this study the IACHT therapeutic option was epirubicin plus cisplatin administered as IACHT, in association with oral capecitabine (ECX) or intravenous 5-fluorouracil (ECF) administered as SCHT. ECF was used in the first part of the study. Then ECX was preferred, when the capecitabine was shown to have a similar efficacy of the continuous infusion of 5-FU, and the oral administration was easier. This new schedule was better administrable, because it did not require an infusion pump. ECX was also better appreciated by patients. They required less time and number of hospitalizations.

SCHT regimens were ECX that was used in 113 patients (78%) and ECF that was adopted in 32 patients (22%).

ECX regimen included: a bolus infusion in the hepatic artery with 50 mg/m² of epirubicin in 100 ml of saline solution, and cisplatin 60 mg/m² in 120 ml of 5% glucose solution, and capecitabine 1000 mg/m² given orally twice a day from Day 1 to Day 14. A rest of a week was performed. IACHT-SCHT was repeated for at least three cycles or till progression if tolerated. Tumor response was monitored every three cycles and the treatment was continued until disease progression.

ECF regimen included: a bolus infusion in the hepatic artery with 50 mg/m² of epirubicin in 100 ml of saline solution, and cisplatin 60 mg/m² in 120 ml of glucose solution, and 200 mg/m² per day of 5-fluorouracil that was administered by intravenous continuous infusion through a central venous catheter from Day 1 to Day 14. A rest of a week was performed. IACHT-SCHT was repeated for at least three cycles or till progression if tolerated.

Tumor response was monitored every three cycles and the treatment was continued until disease progression. When PR or CR was reached, patients were switched to maintenance.

Patients, who had CR or PR after IACHT-SCHT received maintenance CHT with gemcitabine-based scheme until disease progression. Gemcitabine was administered at the dosage of 1000 mg/m² on days 1, 8 and 15, every 4 weeks for at least six cycles or until disease progression [6]. Tumor response was assessed every three months until evidence of clinical progression.

We performed the maintenance therapy only when clinically indicated, including fit patients, that had responded to previous IACHT and had better survival expectancy, because they could bear the therapy. Unfit patients and patients that did not respond to IACHT were treated according to best supportive and palliative care, as they were not clinically indicated to continue

the chemotherapy.

• **Tolerability**

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 was used to monitor the safety.

• **Tumor response**

CT scan and/or MRI were performed every 3 months to assess tumor response, applying the RECIST 1.1. Initial values of greatest diameter of viable tumor against greatest total tumor diameter were compared with those observed 3 months after treatment. Clinical visits, laboratory testing for blood counts, liver functionality and tumor marker levels (carbohydrate antigen 19–9: CA 19–9) were made monthly.

• **Statistical analysis**

Data of the whole sample (n = 145) were analyzed, and descriptive statistics was used for continuous

data that were reported as mean ± standard deviation. Proportions were expressed in percentage. χ^2 and Student’s t-test were used to assess significance of continuous variables (p < 0.05). Kaplan–Meier method was used for survival.

Results

• **The sample**

The study included 145 patients with average age of 62 years. Seventy eight of these (54%) were males and 67 (46%) females (Table 2). All 145 patients received IACHT-SCHT. SCHT regimen included ECX that was used in 113 patients (78%) and ECF that was used in 32 patients (22%).

Twenty six (18%) patients had clinical improvement (CR or PR) to IACHT-SCHT and received maintenance with gemcitabine-based protocol. The remaining 119 (82%) patients received only IACHT-SCHT. The IACHT-SCHT group included 28 (24%) ECCA patients (bile duct and gallbladder) and 91 (76%) were ICCA.

Maintenance CHT group included only ICCA. There was no bias, since our trial was done in a routine clinical practice setting and included a potentially broader disease spectrum. ECCA were known to be more aggressive than ICCA and it was difficult to obtain disease control. For these reasons only ICCA arrived to the maintenance therapy step.

• **Tumor response**

Tumor response of the whole sample of 145 patients was PR in 28 (20%) patients and stable disease (SD) in 72 (48%) patients. Progression disease (PD) was in 44 (31%) patients three months after therapy. CR was observed in only one case (1%) after ECX treatment (Figure 1).

There were differences between treatment type: PR was observed in 23 (19%) patients of IACHT-SCHT, and in eight (32%) of maintenance group. PR of maintenance group (32%) did not include response to previous IACHT, but it was the response to maintenance therapy only. SD was observed in 61 (51%) patients of IACHT-SCHT and in ten (37%) of maintenance group. PD was observed in 39 (33%) patients of IACHT-SCHT and eight (32%) of maintenance group. CR was observed in only one (1%) patient of IACHT-SCHT, and none of maintenance group (Figure 1). Eleven patients were brought to resection after IACHT-SCHT (9% downsizing).

We analyzed separately ICCA and ECCA of the IACHT-SCHT sample to study the tumor response of each type of tumor. This analysis

Table 2. The sample.		
n = 145	n	%
Male	78	54
Female	67	46
Age Mean (range)	62.3	(26.3–80.6)
ECOG (n = 120) baseline		
Median	1	
0	55	46
1	45	38
2	20	17
CA 19–9Median IU/ml (range)		
Baseline	140	(0.8–89986)
3 months	89.9	(0–51200)
6 months	34	(0–2000)
Previous surgery/thermoablation		
None	87	60
Surgery	52	36
Chemotherapy/radiotherapy	6	4
Tumor diagnosis		
Cholangiocarcinoma	114	78
Gallbladder carcinoma	20	14
Choledochus	11	8
Metastases		
Liver	105	
Lymph nodes	17	11
Peritoneum	11	7
Lung	5	3
Bones	4	3
Other	3	2

Figure 1. Tumor response after 3 months of therapy.

CR: Complete response; IACHT-SCHT: Intra-arterial chemotherapy-systemic chemotherapy ; PD: Progression disease; PR: Partial response; SD: Stable disease.

showed that the ECCA group had PR in 11 (39%) patients, SD in 13 (46%) and PD in three (11%). Only one (4%) had CR in the ECCA group. Forty-nine (53%) patients had PR, 26 (29%) had SD and 16 (18%) had PD in the ICCA group.

No comparisons were made between ICCA and ECCA because, from data of the literature, they were not comparable diseases [2,3].

• Overall survival

Median follow-up time was 52.7 months for IAHCT and SCHT groups (range 3–60). Median OS was 12.82 (95% CI:1.9–29.5) and 21.30 (95% CI:2.1–28.7; $p < 0.05$) months for respectively IACHT-SCHT and maintenance group (Figures 2 & 3). Survival was 46% for IACHT-SCHT group at 1 year after treatment.

Median time to progression (TTP) was 5.6 (95% CI:0.9–18.4) months and overall time to progression (OTTP) was 9.1 (95% CI:1.6–28.0) months for IACHT-SCHT. TTP was 7.1 months (95% CI:3.00–11.00; $p < 0.05$) and OTTP was 12.5 months (95% CI:4.4–14.2; $p < 0.05$) for the maintenance group.

The OS analysis of ICCA and ECCA groups showed that median OS was 11.8 (95% CI:8.3–38.6) and 10.9 (95% CI:3.4–11.5) months for

ICCA and ECCA group, respectively.

Six out of 11 downstaged patients were resected and five were thermoablated. Their median survival from diagnosis was 44.8 months. One of the resected patients is still alive 4.5 years from surgery, and is free from disease. Survival of these patients was 100% at 1 year, 70% at 2 years, 52% at 3 years and 35% at 4 years.

• Tolerability

Adverse events of mild moderate (G1–2) intensity were: anemia (24%), nausea and vomiting (33%), alopecia (60%), leucopenia (21%) and fever (18%; Table 3). Adverse events of G3 intensity were observed in 5% of the whole sample as reported in Table 3. IACC and ECCA had similar toxicity. No serious adverse events was observed.

Discussion

Cholangiocarcinoma has a poor prognosis, mostly because the symptoms of the disease appears when it is already in an advanced stage. Patients are often unresectable and late in disease progression already at diagnosis. Surgical resection is the only curative option. It is possible in only about 30% of patients due to the presence of locally advanced disease, distant metastases or comorbidity in elderly patients [20–22].

Figure 2. Overall survival after first line therapy.

CR: Complete response; ECCA: Extrahepatic group; ICCA: Intrahepatic-cholangiocarcinoma group; PD: Progression disease; SD: Stable disease.

The recurrence rate after surgery is about 85% within 3 years after resection [22].

The current recommended first line chemotherapy for advanced cholangiocarcinoma is the combination of gemcitabine and a platinum compound [6,18,23]. Systemic chemotherapy has only limited benefit, and even if chemotherapy regimens have recently improved survival, OS

after gemcitabine plus cisplatin therapy is still <1 year, because most cholangiocarcinoma patients develop distant metastases [19]. The literature has few studies on systemic CAA treatments and most of them do not give clear results on efficacy correlated to patients profile. For this reason it is difficult to draw conclusion if it is better use of systemic or locoregional therapies.

Lack of information is available for maintenance chemotherapy for cholangiocarcinoma. For this reason the present study reported innovative data. The results showed a median OS of 12.82 (95% CI:1.9–29.5) and 21.30 (95% CI:2.1–28.7) months for respectively IACHT-SCHT and maintenance groups, respectively. Overall response was 20% for IACHT-SCHT and 32% for maintenance. Overall response of the maintenance group (32%) did not include response to previous IACHT, but it was the response to maintenance therapy only. These results were in agreement with previous studies that used cisplatin in combination with a bolus of 5-FU and epirubicin. They obtained tumor RR ranging from 10 to 35% and median OS of 11 months [10,20,21]. OS observed in this study was similar to that obtained after curative surgical resection (median OS of 27–36 months) [22] and better than that reported by Valle *et al.* of 11.7 months from the ABC-02 trial [6].

Figure 3. Overall survival after maintenance therapy.

ALL: Whole ICHT SCHT; ECA: Extrahepatic biliary cancer; ICCA: Intrahepatic cholangiocarcinoma.

Median TTP was 5.6 (95% CI:0.9–18.4) months and OTTP was 9.1 (95% CI:1.6–28.0) for IACHT-SCHT. TTP was 7.1 months (95% CI:3.00–11.00) and OTTP was 12.5 months (95% CI:4.4–14.2) for the maintenance group. These results were close to the 10 months reported by other studies [16,19]. The analysis of tumor response, OS and time to progression of ICCA and ECCA showed similar results with other published studies [9,10,24–26] and confirmed the better outcome of ICCA.

The IACHT-SCHT group included 28 (24%) ECCA patients and 91 (76%) were ICCA, the responding patients who entered the maintenance were only ICCA. Another important results were that 11 patients were brought to resection after IACHT-SCHT (9% downsizing). Six of them were resected and five thermoablated. Their median survival was 44.8 months, with 100, 70, 52 and 35% of survival at 1, 2, 3 and 4 years respectively. One of the resected patients was free from disease and still alive 4.5 years from surgery. Survival of these patients was 100% at 1 year. This is an interesting result that has never been reported by any other study. For this reason the maintenance therapy in fit patients may be a valid tool to increase survival, and need further investigation.

The maintenance chemotherapy used the sequential therapy adopting noncross-resistant gemcitabine-based schedule in this study. The benefits of maintenance were also observed in other types of tumor such as non-small-cell lung cancer and urotelial tumors [11,12]. Further studies are required to confirm this benefit.

The maintenance could not be performed in unfit patients that were not clinically indicated to continue the chemotherapy and they were treated according to best supportive and palliative care. For this reason the maintenance was performed only to those that responded to IACHT in order to prolong the benefits obtained with IACHT, as it was obtained with a prolonged survival.

The maintenance chemotherapy was used with interesting results in tumor response, improvement of survival and progression delay: median OS was 21.30 versus 12.1 months of IACHT-SCHT, the OR was 32% versus of 20% for first line CHT, and 7.1 versus 5.6 months of TTP of IACHT-SCHT. These differences were not statistically significant because of the small number of patients in the maintenance in respect to IACHT-SCHT. They may suggest a possible advantage of the maintenance for cholangiocarcinoma. First line with IACHT-SCHT

Table 3. Adverse events.

Adverse event	%
Alopecia	60
Nausea and vomiting	33
Anemia	24
Leucopenia	21
Fever	18

followed by gemcitabine-based maintenance therapy for ICCA may be useful to increase survival.

Conclusion

The results of this study suggest that patients with unresectable cholangiocarcinoma may benefit from IACHT-SCHT and maintenance therapy that were well tolerated and improved survival. Future studies on maintenance therapy are required to confirm the efficacy in tumor response and survival with a larger number of patients

Future perspective

It is not know the correct sequence or the best treatment option for CCA, especially concerning second line treatment. Maintenance therapy may be a new approach for patients who respond to first line treatment. Future studies are required to assess the efficacy of IACHT-SCHT followed by maintenance therapy, or in combination with other liver directed therapies (local ablation with radio frequency ablation or microwave, and transcatheter arterial chemoembolization).

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

SUMMARY POINTS

- Histologically confirmed diagnosis of nonresectable cholangiocarcinoma was necessary for inclusion in the study.
- Intra-arterial chemotherapy (IACHT) therapeutic options were epirubicin plus cisplatin administered as IACHT, in association with oral capecitabine (ECX) or intravenous 5-fluorouracil (ECF) administered as systemic chemotherapy (SCHT).
- ECX regimen included: a bolus infusion in the hepatic artery with 50 mg/m² of epirubicin in 100 ml of saline solution, and cisplatin 60 mg/m² in 120 ml of 5% glucose solution, and capecitabine 1000 mg/m² given orally twice a day from Day 1 to Day 14.
- ECF regimen included: a bolus infusion in the hepatic artery with 50 mg/m² of epirubicin in 100 ml of saline solution, and cisplatin 60 mg/m² in 120 ml of glucose solution, and 200 mg/m² per day of 5-fluorouracil that was administered by intravenous continuous infusion through a central venous catheter from Day 1 to Day 14.
- A rest of a week was performed from day 14 to 21 and then the cycle was repeated for at least threefold or till progression if tolerated.
- Tumor response was monitored with CT scan every three cycles.
- The maintenance treatment was continued until disease progression.
- Patients, who had complete response or partial response after IACHT-SCHT and received maintenance CHT with gemcitabine-based scheme until disease progression.
- Patients with unresectable intrahepatic cholangiocarcinoma and extrahepatic biliary cancer may benefit from IACHT-SCHT therapy.
- Partial response was 19% in IACHT-SCHT; 32% in maintenance CHT.
- Stable disease was 51% in IACHT-SCHT and 37% in maintenance CHT.
- Adverse events of moderate (G2) intensity were: anemia (24%), nausea and vomiting (33%), alopecia (60%), leucopenia (21%) and fever (18%).
- Overall survival was 12.82 (95% CI:1.9–29.5) and 21.30 (95% CI:2.1–28.7) months for respectively IACHT-SCHT and maintenance CHT.
- Median time to progression was 5.6 (95% CI:0.9–18.4) months and overall time to progression was 9.1 (95% CI:1.6–28.0) for IACHT-SCHT.
- Time to progression was 7.1 months (95% CI:3.00–11.00) and overall time to progression was 12.5 months (95% CI:4.4–14.2) for the maintenance group.

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