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Chemotherapy in biliary tract cancer

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Abstract. – *Background:* **Biliary Tract Cancer is a rare and aggressive tumor characterized by unresponsiveness to chemotherapy and radiotherapy in the vast majority of cases. Surgery offers the only possibility of a cure, though post-operative disease recurrence is common. Only few randomized trials with few patients have been conducted to in this setting of patients and standard chemotherapy has not been established yet.**

Results and Conclusions: **This article summarizes the most important clinical trials regarding chemotherapy for biliary tract cancer and the first evidences regarding the adjuvant treatment. Moreover the clinical trials evaluating targeted therapy will be described, especially those assessing the role of anti-EGFR and antiangiogenic agents.**

Key Words:

Biliary tract cancer, Chemotherapy, Targeted therapy.

Abbreviatons

BTC = Biliary Tract Cancer
EGFR = Epidermal Growth Factor Receptor
GEMOX = Gemcitabine-Oxaliplatin
OS = Overall Survival
PD = Progressive Disease
PFS = Progression-Free Survival
RR = Response Rate
PR = Partial Response
SD = Stable Disease
VEGF = Vascular Endothelial Growth Factor

Background

The term biliary tract cancer (BTC) includes both cholangiocarcinoma and carcinoma arising from the epithelial lining of the gallbladder and bile ducts (intrahepatic, perihilar and distal biliary tree cancers). The "Classification of Biliary Tract Carcinoma" has considered bile duct cancer, gallbladder cancer, and ampullary cancer as BTCs. Epidemiological features are different between intrahepatic and extrahepatic cholangiocarcinoma. In fact the incidence and mortality rates of intrahepatic cholangiocarcinoma have been increasing, whereas the incidence of extrahepatic cholangiocarcinoma is constant and mortality rates have been decreasing[1]. Radical surgery is the only possibility for cure, but only 10% of patients can be operated and recurrence rates are high. Patients with unresectable or metastatic BTC have a poor prognosis with a median overall survival (OS) time of 1 year. Clinical trials are evaluating different therapeutic approaches for these patients, but because of the small numbers of patients and heterogeneous patient population most of the clinical data are derived from phase II trials. In fact only few Phase III trials have been conducted[2].

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A multi-center retrospective analysis evaluated the survival benefits of chemotherapy versus best supportive care in a mixed population of pancreatic and BTC patients. This study showed that an association of 5-fluorouracil (5-FU) plus leucovorin (LV) and etoposide therapy increased survival in patients with intrahepatic cholangiocarcinoma (8.44 months), extrahepatic Cholangiocarcinoma: (10.15 months) and gallbladder cancer (6.50 months) versus best supportive care ($p < 0.0001$)[3]. Many Phase II clinical trials have been conducted to establish the most effective combination in patients with BTC.

5-FU and 5-FU-based regimens were the first schedules tested. Trials evaluating combination therapy with cisplatin showed response rates of 10%-40% and median overall survival (OS) better than those observed with 5-FU alone[4]. Phase II studies of capecitabine plus cisplatin in BTC demonstrated RRs of 21-40%[5]. Single-agent gemcitabine obtained RRs of 0%-30%, with median OS times in the range of 5-14 months.

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Based on good tolerability and promising RRs and OS times, recent studies have evaluated the combination of gemcitabine with other agents. Phase II clinical trials have evaluated gemcitabine and cisplatin or oxaliplatin combinations with RRs ranging between 21% and 53% and median OS times ranging between 5 and 15 months. Gemcitabine has also been evaluated in combination with 5-FU[2]. The combination of Gemcitabine and capecitabine showed a median OS time of 12.7 months and RRs of 29%[6]. A recent pooled analysis of 104 chemotherapy trials involving 1,368 BTC patients suggested a biologic difference between cholangiocarcinoma and gallbladder carcinoma and pointed toward gemcitabine as the most active agent subgroup analysis of gallbladder carcinoma versus cholangiocarcinoma demonstrated a significantly greater RR in gallbladder carcinoma patients (36% vs 18%), whereas the median OS time was better for patients with cholangiocarcinoma (9.3 vs 7.2)[7]. The only phase III trial in BTC has compared etoposide, 5-FU, and leucovorin (FELV) with epirubicin, cisplatin, and 5-FU (ECF). Only 54 of the planned 119 patients have been recruited. The median OS for ECF was 9.02 months versus 12.03 months for FELV (p=0.2059). Objective RRs were similar: 19,2% for ECF versus 15% for FELV[8]. To date, the standard regimen for patients with BTC has not been established, in fact only modest activity have been demonstrated with standard chemotherapy. Based on the current literature many schedules can be proposed for patients with advanced biliary tract cancer. Patients with a good performance status can benefit from combination chemotherapy, which consists of gemcitabine and 5-FU/FA (or capecitabine) or a platinum analog. These schedules may yield response rates between 20% and 30% and offer median survival rates of 8-12 months. The combinations of Gemcitabine/Oxaliplatin and Gemcitabine/fluoropyrimidines offer the same activity of the combination Gemcitabine/Cisplatin with a better safety profile[2].

Targeted Therapy in Biliary Tract Cancer

Recently, the biology of bile duct cancer has been extensively studied. The carcinogenic process includes the transformation of normal bile duct cells in cancer cells. BTCs are characterized by many mutations in cancer-related genes: activation of KRAS (mutated in 45% of BTC), loss of function of the P16, INK4A, P53, and SMAD4 tumor suppressor genes and activation of BRAF (mutated in 22% of cholangiocarcinomas). Epidermal growth factor receptor (EGFR) has been shown to be activated by bile acids and induces cyclooxygenase-2 expression that may contribute in the development of BTC. Preclinical studies have shown that antibodies anti-EGFR caused an inhibition of cell proliferation, increasing apoptosis. Due to the limited efficacy of chemotherapy in patients with BTCs, clinical trials are evaluating targeted therapy in patients with BTCs. Anti-EGFR therapies seem to be effective in BTCs, especially if combined with chemotherapy or with other biological agents. A multicenter, randomized phase II trial in patients with advanced BTC (BINGO trial) is

Table I. Clinical studies of EGFR inhibitors in BTCs.

Author (Year)	Regimen	Phase	N. patients	Line	Results
Philip et al. (2006)	Erlotinib	II	42	I/II	RR: 7%; PFS (6 months): 17%
Paule B et al. (2007)	Cetuximab+ GEMOX	II	9	II (PD after GEMOX)	Median TTP: 4 months Median OS: 7 months
Malka D et al. (2009)	Cetuximab+ GEMOX vs GEMOX	II	101	I	PFS (4 months): 61% vs 44%
Gruenberger B et al. (2009)	Cetuximab+ GEMOX	II	30	I	RR: 63% Median PFS: 8.3 months Median OS: 12.7 months No correlation between K-Ras and response
Ramanathan et al., ASCO 2006	Lapatinib	II	17	I/II	RR: 0%

Table II. Clinical studies of VEGF inhibitors in BTCs.

Author (year)	Regimen	Phase	N. patients	Results
Clark JV et al. (2007)	Bevacizumab+Gemox	II	24	PR: 7; SD: 6
Zhu AX et al. (2009)	Bevacizumab+Gemox	II	35	PR: 45%; SD: 34%; PFS: 7 months; OS: 13.2 months
El-Khouery et al. (2007)	Sorafenib	II	31	PR: 6%; SD: 29%; PFS: 2 months; OS: 6 months

evaluating the efficacy of GEMOX alone or in combination with biweekly cetuximab in first-line. The primary end-point is PFS at 4 months. Secondary endpoints are RR, PFS, OS, toxicity, early response assessment by Positron Emission Tomography (PET) and blood/tumor EGFR signalling pathway member analyses. From October 2007 to October 2008, 101 patients were enrolled. At the interim analysis, the 4-month PFS rate was 44% versus 61% in the arm with cetuximab, so the addiction of cetuximab to GEMOX showed promising activity. VEGF is overexpressed in cholangiocarcinomas with differences between intra- and extrahepatic cholangiocarcinoma. Phase II trials have evaluated the activity of bevacizumab and sorafenib in BTC with promising results, but Phase III trials of antiangiogenetic agents in combination with chemotherapy have to be conducted to confirm these results. In 2006 the first evidence regarding the activity of bevacizumab in cholangiocarcinoma was published. Some interesting studies of antiangiogenic therapy in patients with BTC have been conducted. A multicenter phase II trial tested the combination of bevacizumab with gemcitabine and oxaliplatin in BTC patients. Among the 23 patients analyzed, 17 had PRs, 5 had SD and one had Progressive Disease (PD) Other potential targets are Akt/mTOR pathway, Ras/Raf//MAPK pathway and the proteasome, with intriguing preclinical evidences Tables I and II show the clinical trials evaluating EGFR and VEGF inhibitors in patients with BTCs[9].

Adjuvant Chemotherapy in BTC

Complete surgical resection is the only treatment offering a chance for cure in patients with BTC. However, many patients experience recurrent disease, locoregional or metastases. Adjuvant treatments has been evaluated in phase III studies, even if patients with periampullary and pancreatic cancer have also been considered. Many small studies suggested some benefit from adjuvant chemotherapy, but a consistent benefit has not been demonstrated. The role of adjuvant chemotherapy after resection of intrahepatic, extrahepatic cholangiocarcinoma or gallbladder cancers has not yet been established and larger clinical trials are needed.

Conclusions

Conventional chemotherapy have achieved only modest results in patients with BTC. Heterogeneity in chemotherapy response, genetics and OS among cholangiocarcinomas and gall bladder cancer was shown, so future trials should stratify these entities or include only a specific tumor. New approaches are needed to obtain significant results. The advantage of targeted therapies is an higher tumor cell specificity and efficacy, combined with acceptable toxicity and side effects. These novel combination treatments will enlarge the therapeutic strategies for patients with BTCs, so the results of the ongoing clinical studies are keenly awaited. Phase III trial evaluating the combination of chemotherapy and biological therapy are needed. To date, these drugs as monotherapy or combined with conventional citotoxic drugs have obtained interesting results. The future will be the combination between targeted drugs inhibiting different pathways.

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