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REVIEW ARTICLE

The role of chemotherapy in biliary tract carcinoma

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Abstract
Cholangiocarcinoma is a rare malignancy associated with poor prognosis and high mortality. Surgical resection is the only chance for cure depending on careful patient selection. There are no well-conducted studies regarding the role of adjuvant chemotherapy. Preliminary data suggest that liver transplantation could offer long-term survival in selected patients when combined with neoadjuvant chemoradiotherapy. The literature regarding treatment results with specific regimens in the adjuvant setting is limited and no general recommendation can be given. In patients with locally advanced or metastatic disease, most studies are small, non-randomized phase II trials, and many studies comprise a mix of bile duct cancers, gallbladder cancer, and either pancreatic or hepatocellular cancers. In metastatic cancer, phase II studies with several cytotoxics, including gemcitabine, the platinums, and the fluoropyrimidines, have shown a modest and often short-lasting activity. No single chemotherapy agent or combination regimen can therefore be recommended as a standard of care at present. In this review, we give an overview of chemotherapy in the adjuvant, neoadjuvant, and advanced settings.

Introduction

Five-year survival rates are 5–10% for patients with gallbladder carcinoma and 10–40% for those with cholangiocarcinoma [1]. The treatment of a patient with cholangiocarcinoma should be the subject of a multidisciplinary approach. The lack of randomized trials in the field renders the decision-making process difficult. Based on retrospective series of patients with cholangiocarcinoma, resection can certainly offer cure depending on the extent of the disease and quality of the surgery. We review the impact – if any – of chemotherapy in the adjuvant, neoadjuvant, and advanced setting.

Adjuvant chemotherapy following surgery with curative intent

The only treatment that offers a chance for cure in patients with bile tract cancer is complete surgical resection. Case series in expert and high volume centers have demonstrated that extensive surgery is possible with acceptable morbidity and mortality [2]. However, many patients suffer from recurrent disease, either locoregional or metastases. Adjuvant chemo-(radio)therapy has been studied in phase III studies, but mixing up patients with periampullary and pancreatic head cancers [3]. There have been several small studies suggesting some benefit from adjuvant chemotherapy in certain subgroups, but a consistent benefit has not been demonstrated for adjuvant. A recent update from a larger study of adjuvant chemoradiotherapy did not show a benefit versus observation [4]. There are no well-conducted studies regarding the role of adjuvant chemotherapy following resection of intrahepatic, extrahepatic cholangiocarcinoma or gallbladder cancers. These studies are difficult to perform.

In daily clinical practice, patients at our center are followed clinically and undergo 6-monthly computed tomography (CT) of the abdomen to detect early recurrence.

Chemotherapy in patients with advanced biliary tract cancer

More than 10 years ago, a Scandinavian group published a randomized trial of chemotherapy (5-fluorouracil, folinic acid ± etoposide) versus best

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Table I. Selection of phase II studies of monochemotherapy in advanced biliary tract cancer.

	Location	*n*	Response rate (%)	Progression free survival (months)	Overall survival (months)
5-Fluorouracil/folinic acid					
Chen et al. 1998 [7]	Cholangiocarcinoma	13	33	4	7
	Gallbladder	6			
Choi et al. 2000 [8]	Biliary tract	28	32	NR	6
Gemcitabine					
Kubicka et al. 2001 [9]	Cholangiocarcinoma	23	30	NR	NR
	HCC	20	5	NR	NR
Gallardo et al. 2001 [10]	Gallbladder	26	35	NR	7.5
Park et al. 2005 [11]	Cholangiocarcinoma	15	26.1	8.1	13.1
	Gallbladder	8			
S1 (oral fluoropyrimidine derivative)					
Ueno et al. 2004 [12]	Gallbladder	16	21.1	3.7	8.3
	Cholangiocarcinoma	3			

NR: not reported; HCC: hepatocellular carcinoma.

supportive care in 93 patients with metastatic biliary and pancreatic cancer. The trial questioned the nihilistic attitude adopted by some clinicians [5]. There was an improvement of survival and quality of life (QOL) in the treated group. However, the subgroup of patients with bile duct cancer was too small (37 patients) to yield any significant difference in overall survival (6 months versus 2.5 months). There was a significant benefit though for QOL, with more patients in the treated group having an improved or high QOL (33% versus 5%; $p < 0.001$).

So far, more than 120 trials on chemotherapy for advanced biliary tract cancer have been published since 1985, including nearly 3,000 patients. Most of these trials have been small, non-randomized phase II studies, which were pooled in a recent systematic review [6]. This analysis demonstrated a significant correlation between response rate, disease control rate and overall survival, which is also known for other tumors. Tables I and II summarize the results of a few studies on single agent chemotherapy [7–12] and combination treatment [13–18], respectively. Despite the efforts of some authors, it remains an impossible task to compare these trials because of selection bias. Many studies show a worse survival for patients with gallbladder carcinoma compared to

Table II. Phase II studies of combination chemotherapy in advanced biliary tract cancer.

	Location	*n*	Response rates (%)	Progression free survival (months)	Overall survival (months)
Gemcitabine + oxalipatin					
André et al. 2004 [13]	Gallbladder	11	30		
	Intrahepatic CC	16	21	5.7	15.4
	Extrahepatic CC	4	25		
Gemcitabine + cisplatin					
Kim et al. 2006 [14]	Gallbladder	10	34.5	3	11
	Non-gallbladder CC	19			
Gemcitabine + capecitabine					
Riechelmann et al. 2007 [15]	Gallbladder	27	29	6.2	12.7
	Non-gallbladder CC	48			
Capecitabine + oxaliplatin					
Nehls et al. 2008 [16]	Gallbladder	27	25	4.7	8.0
	Intrahepatic CC	18	0	2.2	5.2
	Extrahepatic CC	20	30	11.3	16.6
5FU/folinic acid + cisplatin					
Taieb et al. 2002 [17]	Gallbladder	10	34	6.5	9.5
	Cholangiocarcinoma	19			
S1 + cisplatin					
Kim et al. 2008 [18]	Gallbladder	16	30	4.8	8.7
	Non-gallbladder CC	35			

CC: cholangiocarcinoma.

Table III. Randomized phase II studies of combination chemotherapy in advanced biliary tract cancer.

	Chemotherapy	*n*	Response rates (%)	Progression free survival (months)	Overall survival (months)
Kornek et al. 2004 [19]	MMC + gemcitabine	25	20	4.2	6.7
	MMC + capecitabine	26	31	5.3	9.25
Ducreux et al. 2005 [20]	5-FU	29	7.1	3.3	5.0
	5FU/FA + cisplatin	29	19	3.3	8.0
Rao et al. 2005 [21]	Epirubicin + cisplatin + 5-FU	27	19.2	5.2	9.02
	5FU + FA + etoposide	27	15	7.3	12.03

CC: cholangiocarcinoma; MMC: mitomycin C; 5-FU: 5-fluorouracil; FA: folinic acid.

those with extrahepatic cholangiocarcinoma. In one study with the combination of capecitabine and oxaliplatin, no responses were noted for intrahepatic cholangiocarcinoma, while 27% of patients with other locations had a response [16]. In future phase III studies, patients should be stratified according to location of the primary tumor.

There are only three randomized studies in the setting of advanced biliary tract cancer, and these are summarized in Table III [19–21]. The first study compared two mitomycin C (MMC) combinations and suggested a better activity of MMC + capecitabine than for MMC + gemcitabin [19]. The EORTC trial [20] showed a higher response rate for the combination of cisplatin, 5-FU and folinic acid versus high dose 5-FU, at the cost of more toxicity. The third study was underpowered to show a difference between the two arms [21].

Based on the current literature, it is clear that there are several options that can be proposed for patients with advanced biliary tract cancer. Patients with a good performance status can benefit from combination chemotherapy, which consists of two of the following drugs: gemcitabine, 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. Patients with gallbladder cancer or intrahepatic cholangiocarcinoma do worse compared to those with the extrahepatic cancer locations.

Targeted therapy for advanced biliary tract cancer

Recently, more insights have been gathered on the biology of bile duct cancer, which can occur anywhere on the path between the finest ramifications of the bile duct tree towards the ampulla from Vater. The carcinogenic process includes the transformation of normal bile duct cells or possibly stem cells – through dysplastic lesions – towards cancer. Several abnormalities in tumor suppressor genes (e.g. p16, p27, p53 ...) and oncogenes (beta-catenin, ERK, Ras, c-neu ...) have been identified. Epidermal growth factor receptor (EGFR) has been shown to be activated by bile acids and induces cyclooxygenase-2 expression that may participate in the genesis and progression of cholangiocarcinoma [22]. This increasing knowledge has resulted in two phase II trials with Her2-neu or EGFR inhibitors lapatinib or erlotinib, which have shown little or no activity (0% and 8% responses, respectively) in advanced biliary system adenocarcinomas [23,24]. Interestingly, a small study of cetuximab in 9 patients with tumor resistance to gemcitabine and oxaliplatin (GEMOX) has shown the possibility of reversal of resistance to GEMOX [25].

Multimodality treatment

A remarkable success of a neoadjuvant protocol from the Mayo Clinic has been reported in patients with unresectable hilar cholangiocarcinoma [26]. With the use of pretreatment radiotherapy (including external beam and brachytherapy) and subsequent capecitabine prior to liver transplantation, they could achieve a 5-year actuarial survival of 82%. These results are clearly better than the current results of surgery for resectable cholangiocarcinoma. Only prospective and randomized trials can define the respective contribution of the different components of the approach.

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