ELSEVIER

Critical Reviews in Oncology/Hematology 85 (2013) 136–148

Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Biliary tract carcinomas: From chemotherapy to targeted therapy

Donatella Marino *,[1], Francesco Leone [1], Giuliana Cavalloni, Celeste Cagnazzo, Massimo Aglietta

Department of Medical Oncology, University of Turin Medical School, Institute for Cancer Research and Treatment (IRCC), Str. Provinciale 142, Km 3.95, 10060 Candiolo, Italy

Accepted 22 June 2012

Contents

1. Introduction . . . 136
2. Molecular, genetic and epigenetic events in BTC . . . 137
3. Surgery and adjuvant treatment . . . 139
4. Systemic therapy in advanced disease . . . 139
   4.1. Chemotherapy . . . 139
      4.1.1. Effective combinations: FPD-platinum compounds; GEM-platinum compounds; FPD–GEM . . . 139
      4.1.2. GEM–cisplatin as a new standard of care . . . 141
   4.2. Targeted therapies . . . 142
5. Conclusion . . . 143
   Conflict of interest . . . 144
   Reviewers . . . 144
   Acknowledgments . . . 144
   References . . . 144
   Biographies . . . 148

Abstract

Biliary tract carcinomas (BTC) are a group of tumours arising from the epithelial cells of intra- and extra-hepatic biliaryducts and the gallbladder, characterised by a poor prognosis.

Surgery is the only curative procedure, but the risk of recurrence is high and furthermore, the majority of patients present with unresectable disease at the time of diagnosis. Systemic therapy is the mainstay of treatment for patients who present recurrent or metastatic disease. Progress has been made in the last decade to identify the most effective chemotherapy regimens, with the recent recommendation of the combination of gemcitabine–cisplatin as the standard schedule.

Comprehension of the molecular basis of cholangiocarcinogenesis and tumour progression has recently led to the experimentation of targeted therapies in patients with BTC, demonstrating promising results.

In this review we will discuss the clinical experience with systemic treatment for BTC, focusing on future directions with targeted therapies.

Keywords: Biliary tract carcinoma; Cholangiocarcinoma; Gallbladder carcinoma; Chemotherapy; Targeted therapy

1. Introduction

Biliary tract carcinomas are a group of tumours arising from the epithelial cells of intra- and extra-hepatic biliaryducts and the gallbladder. They can be divided in gallbladder carcinomas (GBC) and cholangiocarcinomas

* Corresponding author. Tel.: +39 011 9933628; fax: +39 011 9933299.
E-mail addresses: donatella.marino@ircc.it (D. Marino), francesco.leone@ircc.it (F. Leone), giuliana.cavalloni@ircc.it (G. Cavalloni), celeste.cagnazzo@ircc.it (C. Cagnazzo), massimo.aglietta@ircc.it (M. Aglietta).
[1] These authors equally contributed to this work.

1040-8428/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.critrevonc.2012.06.006

(CC). The latter includes extrahepatic cholangiocarcinomas (EHC), intrahepatic cholangiocarcinomas (IHC) and Klatskin tumour, a CC occurring at the junction of the right and left hepatic ducts.

Histologically, more than 90% of BTC are well-differentiated and fall into the category of mucin-producing adenocarcinomas; other types, such as squamous cell carcinoma and small cell carcinoma are less common.

Even though BTC is the 2nd second most common primary hepatic tumour, after hepatocellular carcinoma (HCC), it is still considered to be a rare disease in the Western world, with an incidence of 1–2 cases/100,000. On the contrary, these neoplasms are more common in Eastern countries and South America, with up to 96 cases/100,000 [1].

Prognosis for advanced BTC, which is defined as metastatic or surgically unresectable, is very poor, as median overall survival (OS) is generally less than 1 year following diagnosis [2].

In the majority of cases there is no familial predisposition or specific genetic mutation. Hereditary forms, especially for GBC, have been associated with specific syndromes, such as Gardner Syndrome, Hereditary non-polyposis colorectal cancer (HNPCC) and Neurofibromatosis.

However, a number of environmental and pathologic conditions have been identified as probable risk factors. Biliary diseases such as primary sclerosing cholangitis (PSC) [3], cirrhosis, hepato/chole/choledocholithiasis, chronic cholecystitis, chronic non-alcoholic liver disease, and Hepatic C Virus (HCV) infection can all promote neoplastic transformation [4]. In Eastern countries, infection by liver flukes, such as Clonorchis sinensis or Opistorchis viverrini, has proven to be the strongest risk factor.

CC is more common in the 7th decade, with a slight prevalence for men, whereas GBC tends to mainly affect women with a median age of onset at 65 years. This gender difference might be explained with the different prevalence of certain risk factors (e.g. cholelithiasis is more common in women).

2. Molecular, genetic and epigenetic events in BTC

BTC is the result of malignant transformation of cholangiocytes, in which genetic and epigenetic changes are required for transformation, promotion, and progression [5].

In this section we will illustrate the main molecular pathways that are related to cancerous transformation, such as NO, COX2 and EGFR. We also report the incidence of specific, key role gene mutations in BTC. Finally we provide an outlook on the newest perspectives in molecular research.

Fig. 1 summarises the most important molecular events involved in carcinogenesis. Chronic inflammation is the main risk factor that contributes to the pathogenesis of this kind of neoplasm, as it induces cholangiocytes to produce chemokines and cytokines. This signal cascade results in promotion of growth and survival advantages: the subsequent activation of nitric oxide (NO) or cyclooxygenase-2 (COX2) pathways causes damage in the DNA mismatch repair machinery. The resultant DNA damage leads to accumulation of mutations and alteration of genes involved in cell growth, inhibition of apoptosis and promotion of angiogenesis, such as K-RAS, p53, mdm2, waf-1, p16INK4a, DPC4/Smad4 and APC [6–13].

A close relationship exists between COX-2 and Epithelial Growth Factor Receptor (EGFR) family members. In mice models, constitutive expression of ErbB2 and EGFR in gallbladder and biliary tree epithelia results in elevated COX-2 and subsequent development of BTC. Activation of the EGFR pathway may occur via various different mechanisms. It has been demonstrated that TGF-α, commonly contained in bile acids stimulates the activation of EGFR and its downstream pathways [14,15]. These include, among others, enhancement of COX-2 expression and prostaglandin E2 (PGE2) production that, through the PGE2/EP1 receptor, induces transactivation of EGFR. This signalling is, in part, enhanced by Src [16], a tyrosine kinase (TK) implicated in tumour cell proliferation, adhesion and metastasis [17]. Src is also an important mediator of many downstream effects of EGFR [18].

The EGFR pathway regulates the synthesis and secretion of several angiogenic growth factors, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and Interleukine 8(IL-8) [19].

Acquired genetic mutations in the EGFR pathway may be responsible for the activation of carcinogenesis. EGFR-activating mutations in the TK domain are found in about 15% of cases [20,21], and EGFR gene amplifications are detected in 6% of BTC [22].

Other members of the EGFR family, such as ErbB2, may also be intricately involved; for example, overexpression of ErbB2 which is detected in hepatolithiasis and PCS [23,24], has been reported in EHC [25,26], IHC [27,28] and CC in general [29].

The mutational status of K-RAS has been evaluated in several clinical and preclinical studies that are summarised in Table 1. We recently demonstrated that the incidence of K-RAS mutations in Italian patients was low (6.1%) [25]: this is in accordance with other Western studies [30,31]. However, the highest percentage of K-RAS mutations was found in Eastern countries (38–52%) suggesting that geographical differences in aetiology or genetics might explain this variability [32–36].

B-RAF was found to be mutated in 22% of GBC and 33% of European IHC patients [37,38]. In our experience we observed B-RAF mutations in 8.1% of patients, which is generally lower than other reports [25].

Mutational analysis of PI3KCA revealed that hotspot mutations within exons 9 and 20 are rare in BTCs and the frequency ranges from 4% to 9%. Mutations in PTEN were only found in 4% of CC without loss of protein expression [25,39].

The aberrant expression of specific microRNAs (miRNAs), important mediators of posttranscriptional regulation

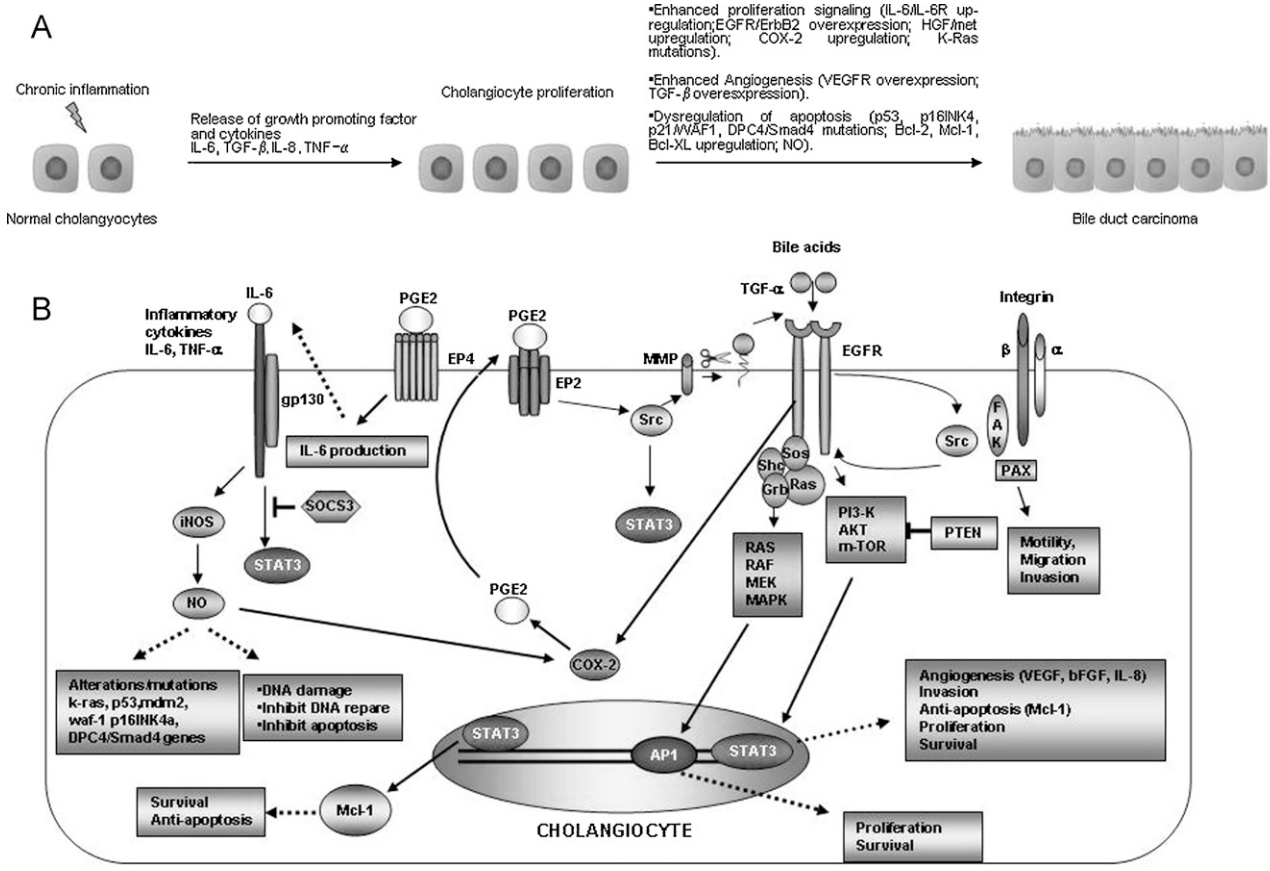

Fig. 1. (A) Multistep pathogenesis of bile duct carcinoma. (B) Molecular events in bile duct carcinogenesis: Pro-inflammatory cytokines induce inducible nitric oxide synthase (iNOS) and COX2. Both iNOS and COX2 induce DNA damage (p53, p16INK4, p21/WAF1, DPC4/Smad4 mutations). Activation of EGFR by TGF-a stimulates MAPK activity, resulting in induction of COX-2 transcription and enhanced synthesis of PGE2. PGE2 can also activate EGFR by an EP2 receptor-dependent mechanism, viaSrc, by stimulating the release of TGF-a. EGFR ligands up-regulate VEGF and other growth factors, which stimulate angiogenesis through the activation of COX-2 and MAPK pathways. Integrins can promote EGFR Src-mediated phosphorylation in the absence of growth factors. The binding of ligands to EGFR results in the direct activation of Src, which might be enhanced in the presence of integrin–FAK-Src complexes. IL6 receptor binds IL6 through gp130 surface molecules. This activation causes dimerization and translocation of Signal Transducer and Activator of Transcription (STAT3) into the nucleus, with consecutive induction of anti-apoptotic genes such as Bcl2 and BclXL. STAT3 also induces transcription of its natural inhibitor SOCS3.

of mRNA, is the most recent development in preclinical research. Several studies are focused on validating the role of miRNAs in BTC. In particular, among the mechanisms of tumour growth sustained by Interleukin 6 (IL-6) [40–44], there is recent evidence for a role of the involvement of miR-148a, miR-152 [45] and miR-370 [46]. Other studies have shown implications of miRNAs in key-role processes of carcinogenesis; miR-21 [47], miR-29b [48] are implicated in inhibition of apoptosis through the modulation of PDCD4, TIMP3 and Mcl-1. miR-141 and miR-200b are overexpressed

Table 1
The incidence of K-RAS mutation in clinical and preclinical studies of BTC.

Author	Year	Country	Site	Percentage of K-RAS mutation	Enrolled patients
Kang JK [33]	1999	Korea	IHC	22.5%	40
Saetta AA [38]	2004	Greece	GBC	25%	21
Suto T [34]	2000	Japan	EHC	9.6%	52
Tsuda H [32]	1992	Japan	CC	56%	9
Boberg KM [3]	2000	Norway	CC	33%	33
Isa T [35]	2002	Japan	CC	39.1%	23
Xu RF [36]	2011	China	CC	38.2%	34
Gruenberger B [30]	2010	Austria	BTC	10%	30
Pignochino Y [25]	2010	Italy	BTC	6.1%	49
Bekaii-Saab T [31]	2011	USA	BTC	8%	28

CC, cholangiocarcinomas; IHC, intrahepatic cholangiocarcinomas; EHC, extrahepatic cholanciocarcinomas; GBC, gallbladder carcinomas; BTC, Biliary tract carcinomas.

in tumour cholangiocytes. In particular, miR-200b dysregulates the protein tyrosine phosphatase non-receptor type 12 (PTPN12), contributing to tumour cell survival, proliferation and response to therapy [49].

3. Surgery and adjuvant treatment

An evaluation of surgical indications and procedures goes beyond the purpose of this review, but it is generally accepted that surgery offers the only chance for cure in both CC and GBC, and should be performed when primary disease is considered resectable; unfortunately the risk of recurrence, even after radical resection is high, with 5-year survival rates in the range of 20–40% of patients [50–52].

Strategies to improve progression free survival (PFS) include both Radiotherapy (RT) and Chemotherapy (CT), which have been investigated alone or in combination in the adjuvant setting. Their role, however, is still undefined, due to the limited number of patients evaluated, the prevalence of retrospective trials and the heterogeneity of stages and types studied. In clinical practice and according to international guidelines, a concurrent chemoradiation treatment with 5-fluorouracil (5FU) or adjuvant CT with 5FU or gemcitabine (GEM) should be considered [53].

4. Systemic therapy in advanced disease

4.1. Chemotherapy

Because of the relatively low incidence of these tumours compared to other more common malignancies, in the past years clinical practice has only been based on small Phase II trials. Many of these have included heterogeneous population of patients, such as pancreatic carcinomas or HCC in addition to BTC, which have made the formulation of a standard of care particularly difficult.

Following Glimelius' randomised trial [54], the first published study that demonstrated a clear benefit of CT over best supportive care (BSC) in pancreatic and biliary cancer, systemic CT has become the mainstay of the treatment plan in patients with unresectable or metastatic disease, as it improves both Quality of Life (QoL) and OS. Some other studies have also confirmed this outcome [55,56].

5FU and other fluoropyrimidines (FPD) have been the backbone of therapy of CC and GBC through the 90s: 5FU, as a single agent or in combination with leucovorin, yields variable Response Rates (RRs) [56–59].

Since the late 90s GEM has been extensively investigated as an effective drug in different cancers; in particular it has demonstrated efficacy both in pancreatic and BTC, pathologies in which it has become of central importance. Phase II clinical trials using single agent GEM in CC and GBC have generally shown satisfactory RRs as well as a good safety profile. Even though these studies have only included a small number of patients, and occasionally different cancer types such as pancreatic and HCC, we can assume that GEM alone yields RRs in about 20% of patients, with an Overall Disease Control Rate (DCR) in approximately two-thirds of the patient population. Indeed, OS is around 8 months, significantly higher than the OS reported in the literature for BSC [60–71].

Combination therapy often included combinations with doxorubicin, mitomycin and, as it will be further elucidated, platinum compounds [72–77].

The use of triplets, and multi-drug therapy in general, has recently proven to be a feasible strategy for fit patients in metastatic pancreatic cancer [78]. Similarly in BTC, the combination treatments GFP (GEM, 5FU, cisplatin), GFO (GEM, 5FU, oxaliplatin), ECF (epirubicin, cisplatin and 5FU) and PEFG (GEM, 5FU, cisplatin, epirubicin) have all been used, with positive outcomes [79–83].

Results of the most representative studies cited above are shown in Table 2.

4.1.1. Effective combinations: FPD-platinum compounds; GEM-platinum compounds; FPD–GEM

Therefore, GEM, FPD and platinum derivatives have all been tested in different combinations. Results are summarised in Table 3. Here we will briefly discuss the results of the most relevant.

The randomised controlled trial (RCT) of Ducreux et al. in 2005 [59] may resume outcomes from fluoropyrimidine and platinum compounds therapy [84–95]: 58 patients were randomised to either receive high-dose 5FU or 5FU, folinic acid and cisplatin. RRs and OS in the combination arm were higher compared to single 5FU therapy (18.5% vs. 7.1% and 8 vs. 5 months) but these results were hampered by higher haematological and gastrointestinal toxicity. The authors concluded that, because of the occurrence of severe side effects in patients with a poor life expectancy, the 5FU-cisplatin combination did not warrant further investigation in a Phase III RCT.

The phase II trial reported by Riechelmann et al. evaluated the combination therapy of gemcitabine and capecitabine [96]: objective response (OR) was observed in 29% of the 75 patients, with 3 patients having a complete response (CR); average OS was 12.7 months. No unexpected or dose-limiting toxicities were evident. Similar results have been observed in other studies combining GEM with capecitabine [97,98] or other FPD [99–104].

Gemcitabine has also been evaluated for combination therapy with either cisplatin, oxaliplatin or, to a lesser extent, carboplatin, with similar RRs in all cases. From greater than 20 Phase II trials we can deduce that on average, DCR is about 55% with platinum combinations, with OS in the range of 8–10 months. Haematological toxicity was a common finding, with variable incidence of anaemia, thrombocytopenia and neutropenia; as predictable, peripheral sensory neuropathy was exclusively noticed in patients treated with

Table 2
Overview on studies of systemic treatment in BTC.

Study		Patients		Drugs	Results	
Author	Year				OR	OS
Sanz-Altamira PM	2001	25		IRI	8%	10 ms
Kubicka S	2001	43	CC 23	GEM	5%	NA
			HCC 20	GEM	30%	NA
Lin MH	2003	24		GEM	12.5%	7.2 ms
Tsavaris N	2004	30		GEM	30.0%	17.1 ms in GBC 11.4 ms in BTC
Park JS	2005	23		GEM	26.1%	13.1 ms
Okusaka T	2006	40		GEM	17.5%	7.6 ms
Taal BG	1993	30		MMC	10%	NA
Androulakis N	2006	29		OXALI	20.6%	7 ms
Papakostas P	2001	25		TXT	20%	8 ms
Malik IA	2003	30		5FU + FA	7%	14.8 ms
Kornek GV	2004	51	Arm A 26	MMC + CAPE	31%	9.25 ms
			Arm B 25	MMC + GEM	20%	6.7 ms
Furuse J	2006	24		U + DOX	12.5%	7.6 ms
Harvey JH	1984	17		5-FU + MMC + DOX	31.0%	NA
Lee S	2009	31		5FU + DOX + MMC	12.9%	6.7 ms
Glimelius B	1996	90	Arm A	5FU + LV + ETP + BSC or 5FU + LV + BSC (elderly & poor PS pts)	NA	6 ms
			Arm B	BSC	NA	2.5 ms
Takada T	1996	83	Arm A 42	5-Fu + DOX + MMC	7.2%	NA
			Arm B 41	BSC	NA	NA
Raderer M	1999	39	Arm A 20	5FU + LV + MMC	25%	9.5 ms
			Arm B 19	GEM	16%	6.5 ms
Rao S	2005	54	Arm A 27	5FU + ETP + LV	19.2%	9.02 ms
			Arm B 27	EPR + CDDP + 5FU	15%	12.03 ms
Kruth J	2010	28		CAPE + TXT + MMC	21.4%	6.8 ms
Feisthammel J	2007	30		IRI + 5FU + FA	10%	166 days in ICC 273 days in GBC
Park SH	2006	43		EPR + CDDP + CAPE	40%	8 ms
Ellis PA	1995	32		EPR + CDDP + 5FU	40% in BTC 29% in HCC	NA
Takada T	1998	83	Arm A 42	FU + DOX + MMC	7.2%	NA
			Arm B 41	BSC	NA	NA
Sharma A	2010	81	Arm A 27	BSC	0%	4.5 ms
			Arm B 28	FU + FA	14.3%	4.6 ms
			Arm C 26	GEM + OXALI	30.8%	9.5 ms
Yamashita Y	2006	8		GEM + 5FU + CDDP	37.5%	23.5 ms
Yamashita Y	2010	21		GEM + 5FU + CDDP	33.3%	18.8 ms
Plyzos A	1996	13		MMC + 5 FU + FA	23%	22 ws
Cereda S	2010	37		CDDP + EPR + 5FU + GEM	43%	12.1 ms
Eckel F	2000	30		CTX + LV + 5FU + TAM	0%	7.3 ms
Park KH	2005	40		EPR + CDDP + U + LV	22.5%	34 ws
Kajanti M	1994	22		EPR + MTX + 5FU + LV	0%	9 ms
Patt YZ	2001	41		CDDP + IFN α-2b + DOX + 5FU	21%	14 ms

OR, overall response; OS, overall survival; CC, cholangiocarcinomas; HCC, hepatocellular carcinoma; 5-FU, 5-fluorouracil; BSC, best supportive care; CAPE, capecitabine; CDDP, cisplatin; IRI, irinotecan; CTX, cyclophosphamide; DOX, doxorubicin; EPR, epirubicin; ETP, etoposide; FA, folinic acid; FU, fluorouracil; GEM, gemcitabine; IFN α-2b, interferon alpha 2-b; L-OHP, oxaliplatin; LV, leucovorin; MMC, mitomycine C; MTX, methotrexate; TXT, docetaxel; U, uracil; TAM, tamoxifen.

Table 3
Overview on trials investigating platinum-based regimens in BTC.

Study		Patients		Drugs	Results					
Author	Year				CR	PR	OR	SD	PD	OS
Kobayashi K	2006	42		5-FU + CDDP	0%	42.9%	42.9%	30.9%	26.2%	NA
Chatni SS	2008	65		5-FU + CDDP	7.69%	26.15%	33.84%	13.85%	32.30%	5.7 ms
Ducreux M	1998	25		5-FU + CDDP	0%	24%	24%	NA	NA	NA
Kim TW	2003	42		CAPE + CDDP	2.40%	19%	21.4%	NA	NA	9.1 ms
Cho JY	2005	44		CAPE + GEM	0%	32%	34%	NA	NA	14 ms
Knox JJ	2005	45		GEM + CAPE	NA	NA	31%	42%	NA	14 ms
Murad AM	2003	26		GEM + 5-FU	3.8%	26.9%	30.7%	NA	NA	9 ms
Malik IA	2003	11	Arm A 8	GEM + CDDP	9%	55%	64%	NA	NA	42 ws
			Arm B 3	GEM						
Ducreux M	2005	58	Arm A 29	5FU	0%	7%	7.1%	46%	NA	5.0 ms
			Arm B 29	5FU, FA + CDDP	4%	15%	19%	44%	NA	8.0 ms
Doval DC	2004	30		GEM + CDDP	13.3%	23.3%	36.60%	23.3%	13.2%	20 ws
Thongprasert S	2005	43		GEM + CDDP	0%	27.5%	27.5%	32.5%	NA	36 ws
Giuliani F	2006	38		GEM + CDDP	3%	29%	32%	21%	47%	8+ ms
Kim ST	2006	29		GEM + CDDP	0%	34.5%	34.5%	13.8%	44.8%	11 ms
Lee GW	2006	24		GEM + CDDP	0%	21%	21%	50%	29%	9.3 ms
Park BK	2006	27		GEM + CDDP	NA	33.3%	33.3%	25.9%	NA	10.0 ms
Charoentum C	2007	42		GEM + CDDP	0%	21%	21%	26%	31%	10.8 ms
Lee J	2008	39		GEM + CDDP	NA	17.1%	17.1%	28.6%	45.7%	8.6 ms
Meyerhardt JA	2008	30		GEM + CDDP	0%	21%	21%	36%	NA	9.7 ms
Goldstein D	2011	50		GEM + CDDP	0%	26%	26%	24%	NA	6.8 ms
Valle JW	2009	86	Arm A 44	GEM	0%	22.6%	22.6%	35.5%	NA	NA
			Arm B 42	GEM + CDDP	0%	27.8%	27.8%	47.1%	NA	NA
Valle J	2010	410	Arm A 204	CDDP + GEM	NA	NA	NA	NA	NA	11.7
			Arm B 206	GEM	NA	NA	NA	NA	NA	8.1
André T	2004	56	Arm A (33) PS 0–2 bilirubin <2.5× normal GEMOX as first-line chemotherapy	GEM + OXALI	NA	NA	36%	26%	39%	15.4 ms
			Arm B (23) PS >2+/or bilirubin >2.5× normal +/or prior chemotherapy	GEM + OXALI	NA	NA	22%	30%	48%	7.6 ms
Wagner AD	2009	72	BTC 37	GEM, OXALI + 5-FU	NA	NA	19%	NA	NA	10.0 ms
			GBC 35	GEM, OXALI + 5-FU	NA	NA	23%	NA	NA	9.9 ms
Harder J	2006	31		GEM + OXALI	0%	26%	26%	45%	29%	11 ms
Verderame F	2006	24		GEM + OXALI	4%	46%	50%	NA	NA	12 ms
Manzione L	2007	34		GEM + OXALI	6%	35%	41%	NA	NA	10 ms
André T	2008	67		GEM + OXALI	0%	14.9%	14.9%	35.8%	NA	8.8 ms
Jang JS	2010	53		GEM + OXALI	1.9%	17%	18.90%	50.9%	NA	8.3 ms
Kim HJ	2009	40		GEM + OXALI	NA	NA	15%	37.2	NA	8.5 ms
Li J	2010	34		GEM + OXALI	3.7%	14.8%	18.5%	66.7%	14.8%	11.6 ms
Sharma A	2010	50		GEM + OXALI	6.2%	15%	21.20%	35.4%	36%	7.5 ms
Williams KJ	2010	48		GEM + CBDCA	NA	NA	31.1%	NA	NA	10.6 ms
Julka PK	2006	20		GEM + CBDCA	21%	15.7%	36.7%	NA	NA	NA

CR, complete response; OR, overall response; OS, overall survival; PD, progression disease; PR, partial response; PS, performance status; SD, stable disease; BTC, biliary tract carcinomas; GBC, gallbladder carcinomas; 5-FU, 5-fluorouracil; CAPE, capecitabine; CBCDA, carboplatin; CDDP, cisplatin; FA, folinic acid; FU, fluorouracil; GEM, gemcitabine; OXALI, oxaliplatin.

oxaliplatin, and liver and renal toxicities were more frequently observed in the case of cisplatin [105–126].

4.1.2. GEM–cisplatin as a new standard of care

Undoubtedly, from this melting-pot of small studies, it has been difficult to determine the optimal treatment for clinical practice.

Pooled analysis by Eckel's et al. [127] evaluated data from 104 trials, with 2810 patients being treated. Analysis of patients who experienced OR or stable disease (SD) pointed to the combination of GEM-platinum compounds as the most effective in terms of RR, DCR, and OS.

These considerations are supported by a recent, small Phase III study by Sharma et al. [56] who randomised 99

patients affected by unresectable GBC to receive: arm A – BSC; arm B – 5FU and folinic acid (FUFa); arm C – modified GEM–oxaliplatin (mGEMOX). Results show significant differences in OR of both CT groups over BSC, with ORs of 0% in arm A, 14.3% in arm B and 37% in arm C ($p = 0.003$). The combination arm was the only treatment to significantly impact on life expectancy: after a median follow-up of 9 months, the FUFa regimen did not prolong OS when compared with BSC (4.5 months vs. 4.6 months), whereas the mGEMOX treatment proved to have a significant benefit, with an OS of 9.5 months ($p = 0.039$).

Suggestions have been turned into a standard of care by recent RCTs. The randomised Phase II ABC-01 trial suggested that the addition of cisplatin to GEM could improve DCR (58.0% for single GEM arm vs. 75.0% of the GEM–cisplatin arm) [128]. Given these results, Valle et al. extended and powered this study to a Phase III trial, the ABC-02 [129]. Eligible patients were affected by metastatic, unresectable or recurrent BTC. Four hundred and ten patients were randomly assigned to receive GEM (1000 mg/m^2 days 1, 8, 15 q 28) or GEM cisplatin (1000 mg/m^2 + 25 mg/m^2 days 1, 8 q 21) for up to 24 weeks of treatment. Primary endpoint was OS. Consistent with previous clinical and preclinical data, the ABC-02 trial confirmed the advantage of combination therapy over GEM alone. Patients who received GEM and cisplatin had an improvement in PFS of 3 months (8.0 months vs. 5.0 months; $p < 0.001$). A clear benefit was also seen for life expectancy, with a median OS of 11.7 months, as compared to 8.1 months for the single agent group ($p < 0.001$); the analysis of pre-specified baseline factors was consistent with these data, regardless of the subgroup taken into account. No significant increase of toxicity was observed between the groups, except for abnormal liver function, which was more frequently noticed in the single agent arm, most likely due to inferior disease control.

The importance of this trial is that it can eventually provide a definite standard regimen for a disease that has been "orphaned" for too long.

Oxaliplatin is widely used in clinical practice instead of cisplatin: the safety profile of the GEMOX regimen and the good RRs discussed above strongly suggest that this is not a suboptimal treatment when compared to the standard schedule with cisplatin.

4.2. Targeted therapies

In recent years we have entered the era of targeted therapies: advances in the comprehension of molecular alterations that promote the development of neoplastic cells have led to new therapeutic modalities that have also recently involved the treatment of BTC.

EGFR family pathway dysregulation has a key role in the development of many types of human cancer, such as pulmonary, breast, colorectal and, as described above, BTC; these alterations may consist of receptor overexpression, amplification, activating mutations in the TK domain, or activation of autocrine growth factor loops.

Different strategies targeting EGFR have been developed such as tyrosine kinase inhibitors (TKIs) or monoclonal antibodies (mAbs) directed against the extracellular domain of the receptor, used alone or in association with CT.

Erlotinib, a small-molecule inhibiting the EGFR TK domain, was approved by the Food and Drug Administration (FDA), in combination with GEM, for the treatment of pancreatic cancer on the basis of a Phase III trial that provided a small, but statistically significant favourable outcome [130]. Its efficacy as a single agent in BTC was evaluated in a Phase II study [131] in which 42 patients received 150 mg oral erlotinib daily. The majority (57%) of patients had already received a first line treatment for metastatic or locally advanced BTC. Three patients (8%) had a confirmed partial response (PR), whereas 17 (43%) achieved a SD for a median of 4.4 months (range 2–20 months). OS was 7.5 months (52% of patients alive after 6 months; 15% at 18 months) and median Time to Progression (TTP) was 2.6 months.

More recently, at the latest American Society of Clinical Oncology (ASCO) meeting, Lim et al. presented a Phase III randomised trial in which GEMOX alone (Arm A), or in combination with erlotinib (Arm B) was evaluated in 268 Korean patients with BTC, also including ampullary carcinomas. Even though no difference in OS and PFS was observed in the whole population, subgroup analysis showed a benefit on PFS of the combination with erlotinib in CC (5.9 months vs. 3.0 months of the GEMOX arm, p 0.049) [132].

Patients were not screened for mutational status of EGFR or KRAS; it is reasonable to believe that results would have been more significant in some of these patient subpopulations.

Lapatinib, a dual EGFR1 and ErbB2 inhibitor, registered for the treatment of HER2 positive breast cancer, has been tested in a Phase II trial including both BTC and HCC, but failed to be efficient [133]: in particular, results for the BTC group are dismal, with a RR of 0%, a median PFS of 1.8 months and median OS of 5.2 months.

Cetuximab, an mAb directed against EGFR appears to be one of the most promising new drugs that could soon be introduced into clinical practice for BTC. A small case series on 5 patients demonstrated excellent responses (1 CR, 3 RP and 1 SD) and correlated with EGFR expression [134].

Gruenberger et al. recently presented a Phase II trial in which cetuximab, combined with GEM and oxaliplatin, was given every 2 weeks for 12 cycles [30]. Among the 30 patients enrolled, OR was achieved in 19 (63%) cases, with 3 CR and 16 PR. The authors underline that 9 patients in the responders group were converted to operable status by treatment, and could thus undergo potentially curative resection, with a striking benefit when compared to the inoperable patients (median PFS was 21.2 months versus 6.8 months). In clinical practice though, conversion rate is not well-defined, because of the significant inter-surgeon and inter-centre variability.

Hopefully, on the basis of these studies, neoadjuvant treatment in BTC is likely to be explored, as well as in colon cancer [135].

Furthermore, molecular analysis revealed that KRAS mutation was a rare finding (10% of patients), which was not directly correlated with failure to treatment as, out of the 3 mutated patients, 2 had a PR (and liver resection in one case) and 1 had SD. On the contrary, a significant correlation was observed between skin toxicity and the response to treatment, with all the patients having grade 2 or 3 skin rash achieving CR or PR, whereas all patients with progression disease (PD) having no rash or grade 1 rash.

The BINGO trial, whose interim results were presented at the ASCO annual meeting in 2009, is a phase II trial in which patients were randomised for receiving GEMOX alone or in combination with cetuximab. In 36 of the 101 patients enrolled, combination therapy seemed to improve PFS rate at 4 months from 44% to 61%, with tolerable toxicity profile [136].

Combination therapy of traditional CT regimens and mAbs against EGFR will be investigated in further trials; according to *Clinicaltrials.gov* six more studies, one of which is chaired by our Institution, will soon yield results of association therapy, not only with cetuximab, but also with panitumumab, a fully humanized mAb targeting EGFR.

Targeting the VEGF pathway, either at the ligand or receptor level, is a consolidated strategy in many human cancers. Bevacizumab, sorafenib and sunitinib are the most common new generation drugs that inhibit this specific signalling.

Zhu et al. presented the results of a Phase II trial [137] in which bevacizumab, administered at as dose of 10 mg/kg biweekly, was added to the GEMOX regimen. Of the 35 patients enrolled, 14 achieved a PR (RR 40%) and 10 an SD. Median OS was 12.7 months and median PFS was 7 months. A reduction of the maximum standardised uptake value (mSUV) assessed by (18F)FDG-PET scan after 2 cycles of therapy correlated with an increased PFS and OS.

The role of bevacizumab still remains unclear because of the lack of a direct comparison with a standard GEMOX arm: data are not strongly superior to those reported in literature for the association of GEM and oxaliplatin without mAbs.

So far, bevacizumab has been used in association with CT. Recently, attempts have been made to combine it with EGFR inhibitors, aiming to produce a synergistic antitumor effect.

This has led to the design of a study using erlotinib (150 mg once daily orally, days 1–28) and bevacizumab (5 mg/kg intravenously every 2 weeks, days 1, 15) [138]. PR was achieved in nine of the 49 evaluable patients, and in six cases (12%) response was prolonged with a median duration of 8.4 months; 25 patients (51%) had SD. Median OS (9.9 months) and TTP (4.4 months) were superior to those expected for erlotinib monotherapy.

Unlike bevacizumab, which binds free VEGF, sorafenib is a small multi-kinase inhibitor with anti-angiogenic activity, as it competitively inhibits VEGFR family (VEGFR 1, 2, 3), and other targets such as platelet-derived growth factor receptor family (PDGFR-b), stem-cell growth factor receptor (c-KIT), Fms-like tyrosine kinase 3 (Flt-3), and the receptor encoded by the ret protooncogen (RET).

In preclinical trials, sorafenib was demonstrated to have anticancer activity in murine models of CC, and occasionally in some case reports [25,139,140]. Despite these good preclinical data, the first Phase II trial of sorafenib monotherapy in advanced BTC has shown low activity profile [141]. Forty-six patients received 400 mg twice a day; 26 of them had already been treated with one or more CT lines. Only 1 patient (2.2%) achieved PR, whereas 14 (30.4%) had SD. Overall, median PFS and OS were dismal, being 2.3 and 4.4 months, respectively.

Further studies will evaluate if the addition of sorafenib to GEM or capecitabine/oxaliplatin can improve outcome. Furthermore, sorafenib will be evaluated in association with erlotinib. Preliminary data of a randomised Phase II trial of GEM plus sorafenib or placebo have been presented at the latest ASCO meeting: the combination therapy shows DCR of 70% (7% PR, 63% SD), with manageable and predictable toxicities [142].

Relatively newer VEGFR inhibitors are being investigated as well: cediranib is a potent anti-angiogenic TKI that has been previously evaluated in different types of cancer, such as glioblastoma, colorectal, lung, renal and prostate with ambiguous results [143–145]. According to *Clinicaltrials.gov* its role in treating BTC is being evaluated in at least two Phase II-III trials in association with cisplatin and GEM.

Similarly, vandetanib is a multi-targeted receptor TKI that inhibits, among others, two key signalling pathways, VEGFR-2 and EGFR. Clinical evaluation of this molecule is being conducted not only for BTC (the VANGOGH trial is already recruiting) but also for other malignancies [146–148].

Targeting the RAS/RAF/MEK/ERK pathway maybe, in the not-too-distant future, a beneficial strategy. A recent publication has shown an interesting role for selumetinib, an inhibitor of MEK1/2 in BTC [31]. Selumetinib was used in pretreated patients in 39% of cases. Even though data are limited by the small number of patients evaluated, only 28 patients (12%) achieved a PR and 68% a SD, which was durable in 56% of cases.

In the literature we also found other studies, some already published, others only recruiting that are testing the efficacy of well-known targeted drugs, such as everolimus or imatinib in BTC. The lack of preclinical bases certainly makes these strategies less attractive than those we have previously outlined [149].

5. Conclusion

We have overviewed the medical treatment of BTC from standard CT to targeted therapies: undoubted progress has been made in understanding the mechanisms of cancer

growth and in detecting effective agents against this type of cancer, especially in the last decade.

Distinguishing BTC from other hepato-pancreatic malignancies has been the first step of this process. As a further clarification, we believe that at least CC and GBC should be considered as different entities: subgroup analysis in many studies suggests that patients affected by GBC have a generally worse outcome. The pattern of recurrence after radical resection is also different, with local relapse being more common in hilar CC and distant in GBC [150]. Eventually, the comprehension of these slight, but significant, differences might be useful for selection of the most suitable treatment for a specific disease. Similarly, biological analysis may help in pointing out molecular differences among populations, which might be due both to different genetics or aetiology. It is likely that a thorough molecular analysis may further drive studies with drugs with a specific molecular target, both in the advanced and adjuvant setting.

A standard, evidence-based regimen, is now fully recognised; GEM and cisplatin are, nowadays, the only established treatment whose efficacy has proven to be applicable to both Western and Eastern patients [151].

Some issues however still remain unsolved. Firstly, the equivalency between GEM–cisplatin and GEM–oxaliplatin, already accepted in clinical practice, has not been validated in RCT.

The comprehension of the molecular basis of cholangiocarcinogenesis, and the results of preclinical studies should stringently drive clinical research. However, the diffusion of targeted therapies in gastrointestinal malignancies and the availability of new, effective molecules have facilitated their direct clinical development.

EGFR and VEGF are the principal pathways involved in cholangiocarcinogenesis, already being tested in the clinical setting. In our opinion, EGFR pathway is the most likely to give positive clinical results; first of all, preclinical bases for EGFR in BTC are more consolidated than those for VEGF. Preliminary clinical results show a certain activity that needs to be confirmed. Moreover, the presence of already validated predictive factors of response/resistance to anti EGFR is certainly useful to select a potentially responsive population.

VEGF signalling may have a secondary role in cholangiocarcinogenesis. Thus, the availability of a large number of effective inhibitors may justify their direct clinical development in a disease that does not have many therapeutic options,

Patients with BTC should then be invited to participate in clinical trials, as this is the only method to answer unsolved enigmas.

Conflict of interest

Actual or potential conflicts of interest do not exist.

Reviewers

Dr. Michael Montemurro, Head of GI Oncology, CHUV – Vaud University Hospital, Centre Pluridisciplinaire d'Oncologie, Bugnon 46, CH-1011 Lausanne, Switzerland.

Dr. Birgit Gruenberger, Barmherzige Brueder Hospital, Department of Internal Medicine, AT-Vienna, Austria.

Acknowledgments

This work was supported by grants from "Progetti di Ricerca Rete Oncologia Piemonte – Valle d'Aosta" and "Associazione Italiana Ricerca sul Cancro – AIRC 5X1000".

References

[1] Khan SA, Toledano MB, Taylor-Robinson SD. Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. HPB (Oxford) 2008;10:77–82.
[2] Charbel H, Al-Kawas FH. Cholangiocarcinoma: epidemiology, risk factors, pathogenesis, and diagnosis. Current Gastroenterology Reports 2011;13:182–7.
[3] Boberg KM, Schrumpf E, Bergquist A, et al. Cholangiocarcinoma in primary sclerosing cholangitis: K-ras mutations and Tp53 dysfunction are implicated in the neoplastic development. Journal of Hepatology 2000;32:374–80.
[4] Shin HR, Oh JK, Masuyer E, et al. Epidemiology of cholangiocarcinoma: an update focusing on risk factors. Cancer Science 2010;101:579–85.
[5] Alpini GPR, LaRusso NF. The pathobiology of biliary epithelia. In: Arias IM, editor. The liver: biology and pathobiology. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001. p. 421–35.
[6] Jaiswal M, LaRusso NF, Burgart LJ, Gores GJ. Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. Cancer Research 2000;60:184–90.
[7] Jaiswal M, LaRusso NF, Gores GJ. Nitric oxide in gastrointestinal epithelial cell carcinogenesis: linking inflammation to oncogenesis. American Journal of Physiology – Gastrointestinal and Liver Physiology 2001;281:G626–34.
[8] Schottenfeld D, Beebe-Dimmer J. Chronic inflammation: a common and important factor in the pathogenesis of neoplasia. CA: A Cancer Journal for Clinicians 2006;56:69–83.
[9] Wise C, Pilanthananond M, Perry BF, et al. Mechanisms of biliary carcinogenesis and growth. World Journal of Gastroenterology 2008;14:2986–9.
[10] Prawan A, Buranrat B, Kukongviriyapan U, et al. Inflammatory cytokines suppress NAD(P)H:quinone oxidoreductase-1 and induce oxidative stress in cholangiocarcinoma cells. Journal of Cancer Research and Clinical Oncology 2009;135:515–22.
[11] Pinlaor S, Sripa B, Ma N, et al. Nitrative and oxidative DNA damage in intrahepatic cholangiocarcinoma patients in relation to tumor invasion. World Journal of Gastroenterology 2005;11:4644–9.
[12] Tsujii M, DuBois RN. Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2. Cell 1995;83:493–501.
[13] Tsujii M, Kawano S, Tsuji S, et al. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. Cell 1998;93:705–16.

[14] Yoon JH, Higuchi H, Werneburg NW, et al. Bile acids induce cyclooxygenase-2 expression via the epidermal growth factor receptor in a human cholangiocarcinoma cell line. Gastroenterology 2002;122:985–93.
[15] Werneburg NW, Yoon JH, Higuchi H, Gores GJ. Bile acids activate EGF receptor via a TGF-alpha-dependent mechanism in human cholangiocyte cell lines. American Journal of Physiology – Gastrointestinal and Liver Physiology 2003;285:G31–6.
[16] Zhang L, Jiang L, Sun Q, et al. Prostaglandin E2 enhances mitogen-activated protein kinase/Erk pathway in human cholangiocarcinoma cells: involvement of EP1 receptor, calcium and EGF receptors signaling. Molecular and Cellular Biochemistry 2007;305:19–26.
[17] Laird AD, Li G, Moss KG, et al. Src family kinase activity is required for signal tranducer and activator of transcription 3 and focal adhesion kinase phosphorylation and vascular endothelial growth factor signaling in vivo and for anchorage-dependent and -independent growth of human tumor cells. Molecular Cancer Therapeutics 2003;2:461–9.
[18] Quesnelle KM, Boehm AL, Grandis JR. STAT-mediated EGFR signaling in cancer. Journal of Cellular Biochemistry 2007;102:311–9.
[19] De Luca A, Carotenuto A, Rachiglio A, et al. The role of the EGFR signaling in tumor microenvironment. Journal of Cellular Physiology 2008;214:559–67.
[20] Leone F, Cavalloni G, Pignochino Y, et al. Somatic mutations of epidermal growth factor receptor in bile duct and gallbladder carcinoma. Clinical Cancer Research 2006;12:1680–5.
[21] Gwak GY, Yoon JH, Shin CM, et al. Detection of response-predicting mutations in the kinase domain of the epidermal growth factor receptor gene in cholangiocarcinomas. Journal of Cancer Research and Clinical Oncology 2005;131:649–52.
[22] Nakazawa K, Dobashi Y, Suzuki S, et al. Amplification and overexpression of c-erbB-2, epidermal growth factor receptor, and c-met in biliary tract cancers. Journal of Pathology 2005;206:356–65.
[23] Terada T, Ashida K, Endo K, et al. c-erbB-2 protein is expressed in hepatolithiasis and cholangiocarcinoma. Histopathology 1998;33:325–31.
[24] Endo K, Yoon BI, Pairojkul C, et al. ERBB-2 overexpression and cyclooxygenase-2 up-regulation in human cholangiocarcinoma and risk conditions. Hepatology 2002;36:439–50.
[25] Pignochino Y, Sarotto I, Peraldo-Neia C, et al. Targeting EGFR/HER2 pathways enhances the antiproliferative effect of gemcitabine in biliary tract and gallbladder carcinomas. BMC Cancer 2010;10:631.
[26] Zheng J, Zhu YM. Expression of c-erbB-2 proto-oncogene in extrahepatic cholangiocarcinoma and its clinical significance. Hepatobiliary & Pancreatic Diseases International 2007;6:412–5.
[27] Settakorn J, Kaewpila N, Burns GF, Leong AS. FAT, E-cadherin, beta catenin, HER 2/neu, Ki67 immuno-expression, and histological grade in intrahepatic cholangiocarcinoma. Journal of Clinical Pathology 2005;58:1249–54.
[28] Sirica AE. Role of ErbB family receptor tyrosine kinases in intrahepatic cholangiocarcinoma. World Journal of Gastroenterology 2008;14:7033–58.
[29] Kim HJ, Yoo TW, Park DI, et al. Gene amplification and protein overexpression of HER-2/neu in human extrahepatic cholangiocarcinoma as detected by chromogenic in situ hybridization and immunohistochemistry, its prognostic implication in node-positive patients. Annals of Oncology 2007;18:892–7.
[30] Gruenberger B, Schueller J, Heubrandtner U, et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer, a phase 2 study. The Lancet Oncology 2010;11:1142–8.
[31] Bekaii-Saab T, Phelps MA, Li X, et al. Multi-institutional phase II study of selumetinib in patients with metastatic biliary cancers. Journal of Clinical Oncology 2011;29:2357–63.
[32] Tsuda H, Satarug S, Bhudhisawasdi V, et al. Cholangiocarcinomas in Japanese and Thai patients: difference in etiology and incidence of point mutation of the c-Ki-ras proto-oncogene. Molecular Carcinogenesis 1992;6:266–9.
[33] Kang YK, Kim WH, Lee HW, et al. Mutation of p53 and K-ras, and loss of heterozygosity of APC in intrahepatic cholangiocarcinoma. Laboratory Investigation 1999;79:477–83.
[34] Suto T, Habano W, Sugai T, et al. Aberrations of the K-ras, p53, and APC genes in extrahepatic bile duct cancer. Journal of Surgical Oncology 2000;73:158–63.
[35] Isa T, Tomita S, Nakachi A, et al. Analysis of microsatellite instability, K-ras gene mutation and p53 protein overexpression in intrahepatic cholangiocarcinoma. Hepato-Gastroenterology 2002;49:604–8.
[36] Xu RF, Sun JP, Zhang SR, et al. KRAS and PIK3CA but not BRAF genes are frequently mutated in Chinese cholangiocarcinoma patients. Biomedicine and Pharmacotherapy 2011;65:22–6.
[37] Tannapfel A, Sommerer F, Benicke M, et al. Mutations of the BRAF gene in cholangiocarcinoma but not in hepatocellular carcinoma. Gut 2003;52:706–12.
[38] Saetta AA, Papanastasiou P, Michalopoulos NV, et al. Mutational analysis of BRAF in gallbladder carcinomas in association with K-ras and p53 mutations and microsatellite instability. Virchows Archiv 2004;445:179–82.
[39] Riener MO, Bawohl M, Clavien PA, Jochum W. Rare PIK3CA hotspot mutations in carcinomas of the biliary tract. Genes, Chromosomes and Cancer 2008;47:363–7.
[40] Isomoto H. Epigenetic alterations in cholangiocarcinoma-sustained IL-6/STAT3 signaling in cholangio-carcinoma due to SOCS3 epigenetic silencing. Digestion 2009;79(Suppl. 1):2–8.
[41] Isomoto H, Kobayashi S, Werneburg NW, et al. Interleukin 6 upregulates myeloid cell leukemia-1 expression through a STAT3 pathway in cholangiocarcinoma cells. Hepatology 2005;42:1329–38.
[42] Kobayashi S, Werneburg NW, Bronk SF, et al. Interleukin-6 contributes to Mcl-1 up-regulation and TRAIL resistance via an Akt-signaling pathway in cholangiocarcinoma cells. Gastroenterology 2005;128:2054–65.
[43] Park J, Tadlock L, Gores GJ, Patel T. Inhibition of interleukin 6-mediated mitogen-activated protein kinase activation attenuates growth of a cholangiocarcinoma cell line. Hepatology 1999;30:1128–33.
[44] Tadlock L, Patel T. Involvement of p38 mitogen-activated protein kinase signaling in transformed growth of a cholangiocarcinoma cell line. Hepatology 2001;33:43–51.
[45] Braconi C, Huang N, Patel T. MicroRNA-dependent regulation of DNA methyltransferase-1 and tumor suppressor gene expression by interleukin-6 in human malignant cholangiocytes. Hepatology 2010;51:881–90.
[46] Meng F, Wehbe-Janek H, Henson R, et al. Epigenetic regulation of microRNA-370 by interleukin-6 in malignant human cholangiocytes. Oncogene 2008;27:378–86.
[47] Selaru FM, Olaru AV, Kan T, et al. MicroRNA-21 is overexpressed in human cholangiocarcinoma and regulates programmed cell death 4 and tissue inhibitor of metalloproteinase 3. Hepatology 2009;49:1595–601.
[48] Mott JL, Kobayashi S, Bronk SF, Gores GJ. mir-29 regulates Mcl-1 protein expression and apoptosis. Oncogene 2007;26:6133–40.
[49] Meng F, Henson R, Lang M, et al. Involvement of human micro-RNA in growth and response to chemotherapy in human cholangiocarcinoma cell lines. Gastroenterology 2006;130:2113–29.
[50] Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Annals of Surgery 2001;234:507–17 [discussion 517-509].
[51] Zhu AX, Hong TS, Hezel AF, Kooby DA. Current management of gallbladder carcinoma. Oncologist 2010;15:168–81.
[52] Endo I, Shimada H, Tanabe M, et al. Prognostic significance of the number of positive lymph nodes in gallbladder cancer. Journal of Gastrointestinal Surgery 2006;10:999–1007.
[53] Brunner TB, Eccles CL. Radiotherapy and chemotherapy as therapeutic strategies in extrahepatic biliary duct carcinoma. Strahlentherapie und Onkologie 2010;186:672–80.

[54] Glimelius B, Hoffman K, Sjoden PO, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Annals of Oncology 1996;7:593–600.
[55] Takada T, Kato H, Matsushiro T, et al. Prospective randomized trial comparing 1/2 FAM (5-fluorouracil (5-FU) + adriamycin + mitomycin C) versus palliative therapy for the treatment of unresectable pancreatic and biliary tract carcinomas (the 2nd trial in non-resectable patients). Japanese Study Group of Surgical Adjuvant Therapy for Carcinomas of the Pancreas and Biliary Tract. Gan to Kagaku Ryoho 1996;23:707–14.
[56] Sharma A, Dwary AD, Mohanti BK, et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. Journal of Clinical Oncology 2010;28:4581–6.
[57] Choi CW, Choi IK, Seo JH, et al. Effects of 5-fluorouracil and leucovorin in the treatment of pancreatic-biliary tract adenocarcinomas. American Journal of Clinical Oncology 2000;23:425–8.
[58] Falkson G, MacIntyre JM, Moertel CG. Eastern Cooperative Oncology Group experience with chemotherapy for inoperable gallbladder and bile duct cancer. Cancer 1984;54:965–9.
[59] Ducreux M, Van Cutsem E, Van Laethem JL, et al. A randomised phase II trial of weekly high-dose 5-fluorouracil with and without folinic acid and cisplatin in patients with advanced biliary tract carcinoma: results of the 40955 EORTC trial. European Journal of Cancer 2005;41:398–403.
[60] Raderer M, Hejna MH, Valencak JB, et al. Two consecutive phase II studies of 5-fluorouracil/leucovorin/mitomycin C and of gemcitabine in patients with advanced biliary cancer. Oncology 1999;56:177–80.
[61] Penz M, Kornek GV, Raderer M, et al. Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. Annals of Oncology 2001;12:183–6.
[62] Kubicka S, Rudolph KL, Tietze MK, et al. Phase II study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. Hepato-Gastroenterology 2001;48:783–9.
[63] Gallardo JO, Rubio B, Fodor M, et al. A phase II study of gemcitabine in gallbladder carcinoma. Annals of Oncology 2001;12:1403–6.
[64] Lin MH, Chen JS, Chen HH, Su WC. A phase II trial of gemcitabine in the treatment of advanced bile duct and periampullary carcinomas. Chemotherapy 2003;49:154–8.
[65] Tsavaris N, Kosmas C, Gouveris P, et al. Weekly gemcitabine for the treatment of biliary tract and gallbladder cancer. Investigational New Drugs 2004;22:193–8.
[66] Eng C, Ramanathan RK, Wong MK, et al. A phase II trial of fixed dose rate gemcitabine in patients with advanced biliary tree carcinoma. American Journal of Clinical Oncology 2004;27:565–9.
[67] Park JS, Oh SY, Kim SH, et al. Single-agent gemcitabine in the treatment of advanced biliary tract cancers: a phase II study. Japanese Journal of Clinical Oncology 2005;35:68–73.
[68] von Delius S, Lersch C, Schulte-Frohlinde E, et al. Phase II trial of weekly 24-hour infusion of gemcitabine in patients with advanced gallbladder and biliary tract carcinoma. BMC Cancer 2005;5:61.
[69] Gelibter A, Malaguti P, Di Cosimo S, et al. Fixed dose-rate gemcitabine infusion as first-line treatment for advanced-stage carcinoma of the pancreas and biliary tree. Cancer 2005;104:1237–45.
[70] Okusaka T, Ishii H, Funakoshi A, et al. Phase II study of single-agent gemcitabine in patients with advanced biliary tract cancer. Cancer Chemotherapy and Pharmacology 2006;57:647–53.
[71] Milella M, Gelibter AJ, Pino MS, et al. Fixed-dose-rate gemcitabine: a viable first-line treatment option for advanced pancreatic and biliary tract cancer. Oncologist 2010;15:e1–4.
[72] Feisthammel J, Schoppmeyer K, Mossner J, et al. Irinotecan with 5-FU/FA in advanced biliary tract adenocarcinomas: a multicenter phase II trial. American Journal of Clinical Oncology 2007;30:319–24.
[73] Harvey JH, Smith FP, Schein PS. 5-Fluorouracil, mitomycin, and doxorubicin (FAM) in carcinoma of the biliary tract. Journal of Clinical Oncology 1984;2:1245–8.
[74] Lee S, Oh SY, Kim BG, et al. Second-line treatment with a combination of continuous 5-fluorouracil, doxorubicin, and mitomycin-C (conti-FAM) in gemcitabine-pretreated pancreatic and biliary tract cancer. American Journal of Clinical Oncology 2009;32:348–52.
[75] Patt YZ, Hassan MM, Lozano RD, et al. Phase II trial of cisplatin, interferon alpha-2b, doxorubicin, and 5-fluorouracil for biliary tract cancer. Clinical Cancer Research 2001;7:3375–80.
[76] Takada T, Kato H, Matsushiro T, et al. Comparison of 5-fluorouracil, doxorubicin and mitomycin C with 5-fluorouracil alone in the treatment of pancreatic-biliary carcinomas. Oncology 1994;51:396–400.
[77] Eckel F, Lersch C, Assmann G, Schulte-Frohlinde E. Phase II trial of low-dose cyclophosphamide, leucovorin, high-dose 5-fluorouracil 24-hour continuous infusion and tamoxifen in advanced biliary tract cancer. Annals of Oncology 2000;11:762–3.
[78] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. New England Journal of Medicine 2011;364:1817–25.
[79] Cereda S, Passoni P, Reni M, et al. The cisplatin, epirubicin, 5-fluorouracil, gemcitabine (PEFG) regimen in advanced biliary tract adenocarcinoma. Cancer 2010;116:2208–14.
[80] Yamashita Y, Taketomi A, Itoh S, et al. Phase II trial of gemcitabine combined with 5-fluorouracil and cisplatin (GFP) chemotherapy in patients with advanced biliary tree cancers. Japanese Journal of Clinical Oncology 2010;40:24–8.
[81] Wagner AD, Buechner-Steudel P, Moehler M, et al. Gemcitabine, oxaliplatin and 5-FU in advanced bile duct and gallbladder carcinoma: two parallel, multicentre phase-II trials. British Journal of Cancer 2009;101:1846–52.
[82] Yamashita Y, Taketomi A, Fukuzawa K, et al. Gemcitabine combined with 5-fluorouracil and cisplatin (GFP) in patients with advanced biliary tree cancers: a pilot study. Anticancer Research 2006;26:771–5.
[83] Morine Y, Shimada M, Ikegami T, et al. Usefulness of gemcitabine combined with 5-fluorouracil and cisplatin (GFP) in patients for unresectable biliary carcinoma. Hepato-Gastroenterology 2009;56:307–12.
[84] Taieb J, Mitry E, Boige V, et al. Optimization of 5-fluorouracil (5-FU)/cisplatin combination chemotherapy with a new schedule of leucovorin, 5-FU and cisplatin (LV5FU2-P regimen) in patients with biliary tract carcinoma. Annals of Oncology 2002;13:1192–6.
[85] Nehls O, Klump B, Arkenau HT, et al. Oxaliplatin, fluorouracil and leucovorin for advanced biliary system adenocarcinomas: a prospective phase II trial. British Journal of Cancer 2002;87:702–4.
[86] Kim TW, Chang HM, Kang HJ, et al. Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced biliary cancer. Annals of Oncology 2003;14:1115–20.
[87] Hong YS, Lee J, Lee SC, et al. Phase II study of capecitabine and cisplatin in previously untreated advanced biliary tract cancer. Cancer Chemotherapy and Pharmacology 2007;60:321–8.
[88] Sanz-Altamira PM, Ferrante K, Jenkins RL, et al. A phase II trial of 5-fluorouracil, leucovorin, and carboplatin in patients with unresectable biliary tree carcinoma. Cancer 1998;82:2321–5.
[89] Ducreux M, Rougier P, Fandi A, et al. Effective treatment of advanced biliary tract carcinoma using 5-fluorouracil continuous infusion with cisplatin. Annals of Oncology 1998;9:653–6.
[90] Kobayashi K, Tsuji A, Morita S, et al. A phase II study of LFP therapy (5-FU (5-fluorourasil) continuous infusion (CVI) and Low-dose consecutive (Cisplatin) CDDP) in advanced biliary tract carcinoma. BMC Cancer 2006;6:121.
[91] Kim YJ, Im SA, Kim HG, et al. A phase II trial of S-1 and cisplatin in patients with metastatic or relapsed biliary tract cancer. Annals of Oncology 2008;19:99–103.
[92] Nehls O, Oettle H, Hartmann JT, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase II trial. British Journal of Cancer 2008;98:309–15.

[93] Lim JY, Jeung HC, Mun HS, et al. Phase II trial of oxaliplatin combined with leucovorin and fluorouracil for recurrent/metastatic biliary tract carcinoma. Anti-Cancer Drugs 2008;19:631–5.
[94] Chatni SS, Sainani RS, Mehta SA, Mohandas KM. Infusion chemotherapy with cisplatinum and fluorouracil in the treatment of locally-advanced and metastatic gallbladder cancer. Journal of Cancer Research and Therapeutics 2008;4:151–5.
[95] Chen JS, Chao Y, Yang TS, et al. A phase II trial of biweekly oxaliplatin with simplified schedule of 48-h infusion of high-dose 5-fluorouracil and leucorvin for advanced biliary tract carcinoma. Cancer Chemotherapy and Pharmacology 2009;65:151–7.
[96] Riechelmann RP, Townsley CA, Chin SN, et al. Expanded phase II trial of gemcitabine and capecitabine for advanced biliary cancer. Cancer 2007;110:1307–12.
[97] Iyer RV, Gibbs J, Kuvshinoff B, et al. A phase II study of gemcitabine and capecitabine in advanced cholangiocarcinoma and carcinoma of the gallbladder: a single-institution prospective study. Annals of Surgical Oncology 2007;14:3202–9.
[98] Knox JJ, Hedley D, Oza A, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. Journal of Clinical Oncology 2005;23:2332–8.
[99] Boxberger F, Jungert B, Brueckl V, et al. Palliative chemotherapy with gemcitabine and weekly high-dose 5-fluorouracil as 24-h infusion in metastatic biliary tract and gall bladder adenocarcinomas. Anti-Cancer Drugs 2003;14:87–90.
[100] Murad AM, Guimaraes RC, Aragao BC, et al. Phase II trial of the use of gemcitabine and 5-fluorouracil in the treatment of advanced pancreatic and biliary tract cancer. American Journal of Clinical Oncology 2003;26:151–4.
[101] Hsu C, Shen YC, Yang CH, et al. Weekly gemcitabine plus 24-h infusion of high-dose 5-fluorouracil/leucovorin for locally advanced or metastatic carcinoma of the biliary tract. British Journal of Cancer 2004;90:1715–9.
[102] Alberts SR, Al-Khatib H, Mahoney MR, et al. Gemcitabine, 5-fluorouracil, and leucovorin in advanced biliary tract and gallbladder carcinoma, a North Central Cancer Treatment Group phase II trial. Cancer 2005;103:111–8.
[103] Sasaki T, Isayama H, Nakai Y, et al. Multicenter, phase II study of gemcitabine and S-1 combination chemotherapy in patients with advanced biliary tract cancer. Cancer Chemotherapy and Pharmacology 2010;65:1101–7.
[104] Kanai M, Yoshimura K, Tsumura T, et al. A multi-institution phase II study of gemcitabine/S-1 combination chemotherapy for patients with advanced biliary tract cancer. Cancer Chemotherapy and Pharmacology 2011;67:1429–34.
[105] Thongprasert S, Napapan S, Charoentum C, Moonprakan S. Phase II study of gemcitabine and cisplatin as first-line chemotherapy in inoperable biliary tract carcinoma. Annals of Oncology 2005;16:279–81.
[106] Charoentum C, Thongprasert S, Chewaskulyong B, Munprakan S. Experience with gemcitabine and cisplatin in the therapy of inoperable and metastatic cholangiocarcinoma. World Journal of Gastroenterology 2007;13:2852–4.
[107] Malik IA, Aziz Z, Zaidi SH, Sethuraman G. Gemcitabine and Cisplatin is a highly effective combination chemotherapy in patients with advanced cancer of the gallbladder. American Journal of Clinical Oncology 2003;26:174–7.
[108] Doval DC, Sekhon JS, Gupta SK, et al. A phase II study of gemcitabine and cisplatin in chemotherapy-naive, unresectable gall bladder cancer. British Journal of Cancer 2004;90:1516–20.
[109] Andre T, Tournigand C, Rosmorduc O, et al. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. Annals of Oncology 2004;15:1339–43.
[110] Kim ST, Park JO, Lee J, et al. A phase II study of gemcitabine and cisplatin in advanced biliary tract cancer. Cancer 2006;106:1339–46.
[111] Julka PK, Puri T, Rath GK. A phase II study of gemcitabine and carboplatin combination chemotherapy in gallbladder carcinoma. Hepatobiliary & Pancreatic Diseases International 2006;5:110–4.
[112] Lee GW, Kang JH, Kim HG, et al. Combination chemotherapy with gemcitabine and cisplatin as first-line treatment for immunohistochemically proven cholangiocarcinoma. American Journal of Clinical Oncology 2006;29:127–31.
[113] Park BK, Kim YJ, Park JY, et al. Phase II study of gemcitabine and cisplatin in advanced biliary tract cancer. Journal of Gastroenterology and Hepatology 2006;21:999–1003.
[114] Giuliani F, Gebbia V, Maiello E, et al. Gemcitabine and cisplatin for inoperable and/or metastatic biliary tree carcinomas: a multicenter phase II study of the Gruppo Oncologico dell'Italia Meridionale (GOIM). Annals of Oncology 2006;17(Suppl. 7):vii73–7.
[115] Verderame F, Russo A, Di Leo R, et al. Gemcitabine and oxaliplatin combination chemotherapy in advanced biliary tract cancers. Annals of Oncology 2006;17(Suppl. 7):vii68–72.
[116] Harder J, Riecken B, Kummer O, et al. Outpatient chemotherapy with gemcitabine and oxaliplatin in patients with biliary tract cancer. British Journal of Cancer 2006;95:848–52.
[117] Lee J, Kim TY, Lee MA, et al. Phase II trial of gemcitabine combined with cisplatin in patients with inoperable biliary tract carcinomas. Cancer Chemotherapy and Pharmacology 2008;61:47–52.
[118] Manzione L, Romano R, Germano D. Chemotherapy with gemcitabine and oxaliplatin in patients with advanced biliary tract cancer: a single-institution experience. Oncology 2007;73:311–5.
[119] Meyerhardt JA, Zhu AX, Stuart K, et al. Phase-II study of gemcitabine and cisplatin in patients with metastatic biliary and gallbladder cancer. Digestive Diseases and Sciences 2008;53:564–70.
[120] Kim HJ, Lee NS, Lee SC, et al. A phase II study of gemcitabine in combination with oxaliplatin as first-line chemotherapy in patients with inoperable biliary tract cancer. Cancer Chemotherapy and Pharmacology 2009;64:371–7.
[121] Andre T, Reyes-Vidal JM, Fartoux L, et al. Gemcitabine and oxaliplatin in advanced biliary tract carcinoma: a phase II study. British Journal of Cancer 2008;99:862–7.
[122] Sharma A, Mohanti B, Raina V, et al. A phase II study of gemcitabine and oxaliplatin (Oxigem) in unresectable gall bladder cancer. Cancer Chemotherapy and Pharmacology 2010;65:497–502.
[123] Jang JS, Lim HY, Hwang IG, et al. Gemcitabine and oxaliplatin in patients with unresectable biliary cancer including gall bladder cancer: a Korean Cancer Study Group phase II trial. Cancer Chemotherapy and Pharmacology 2010;65:641–7.
[124] Li J, Merl M, Lee MX, et al. Safety and efficacy of single-day GemOx regimen in patients with pancreatobiliary cancer: a single institution experience. Expert Opinion on Drug Safety 2010;9:207–13.
[125] Goldstein D, Gainford MC, Brown C, et al. Fixed-dose-rate gemcitabine combined with cisplatin in patients with inoperable biliary tract carcinomas. Cancer Chemotherapy and Pharmacology 2011;67:519–25.
[126] Williams KJ, Picus J, Trinkhaus K, et al. Gemcitabine with carboplatin for advanced biliary tract cancers: a phase II single institution study. HPB (Oxford) 2010;12:418–26.
[127] Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. British Journal of Cancer 2007;96:896–902.
[128] Valle JW, Wasan H, Johnson P, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study – The UK ABC-01 Study. British Journal of Cancer 2009;101:621–7.
[129] Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. New England Journal of Medicine 2010;362:1273–81.
[130] Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. Journal of Clinical Oncology 2007;25:1960–6.

[131] Philip PA, Mahoney MR, Allmer C, et al. Phase II study of erlotinib in patients with advanced biliary cancer. Journal of Clinical Oncology 2006;24:3069–74.
[132] Lim HYLJ, Chang H, Kim JS, et al. Phase III study of gemcitabine/oxaliplatin (GEMOX) with or without erlotinib in unresectable, metastatic biliary tract carcinoma. Journal of Clinical Oncology 2011;29(Suppl.) [abstr LBA4032].
[133] Ramanathan RK, Belani CP, Singh DA, et al. A phase II study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. Cancer Chemotherapy and Pharmacology 2009;64: 777–83.
[134] Chang PY, Cheng MF, Lee HS, et al. Preliminary experience of cetuximab in the treatment of advanced-stage biliary tract cancer. Onkologie 2010;33:45–7.
[135] Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. The Lancet Oncology 2010;11:38–47.
[136] Malka DFL, Mendiboure J, de la Fouchardiere C, Viret F, Assenat E. A multi-center, randomized phase II trial of gemcitabine and oxaliplatin (GEMOX) alone or in combination with biweekly cetuximab in the first-line treatment of advanced biliary cancer: Interim analysis of the BINGO trial. Journal of Clinical Oncology 2009;27(Suppl.):15s [abstr 4520].
[137] Zhu AX, Meyerhardt JA, Blaszkowsky LS, et al. Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome: a phase 2 study. The Lancet Oncology 2010;11:48–54.
[138] Lubner SJ, Mahoney MR, Kolesar JL, et al. Report of a multicenter phase II trial testing a combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer: a phase II Consortium study. Journal of Clinical Oncology 2010;28:3491–7.
[139] Blechacz BR, Smoot RL, Bronk SF, et al. Sorafenib inhibits signal transducer and activator of transcription-3 signaling in cholangiocarcinoma cells by activating the phosphatase shatterproof 2. Hepatology 2009;50:1861–70.
[140] LaRocca RV, Hicks MD, Mull L, Foreman B. Effective palliation of advanced cholangiocarcinoma with sorafenib: a two-patient case report. Journal of Gastrointestinal Cancer 2007;38:154–6.
[141] Bengala C, Bertolini F, Malavasi N, et al. Sorafenib in patients with advanced biliary tract carcinoma: a phase II trial. British Journal of Cancer 2010;102:68–72.
[142] Moehler MHSCC, Kanzler S, Woerns MA, et al. A randomized, double-blind, multicenter phase II AIO trial with gemcitabine plus sorafenib versus gemcitabine plus placebo in patients with chemotherapy-naive advanced or metastatic biliary tract cancer. Journal of Clinical Oncology 2011;29(Suppl.) [abstr 4077].
[143] Alberts SR, Fitch TR, Kim GP, et al. Cediranib (AZD2171) in patients with advanced hepatocellular carcinoma: a phase II North Central Cancer Treatment Group Clinical Trial. American Journal of Clinical Oncology 2011, http://dx.doi.org/10.1097/COC.0b013e3182118cdf.
[144] Shanafelt T, Zent C, Byrd J, et al. Phase II trials of single-agent anti-VEGF therapy for patients with chronic lymphocytic leukemia. Leukemia and Lymphoma 2010;51:2222–9.
[145] Ramalingam SS, Belani CP, Mack PC, et al. Phase II study of Cediranib (AZD 2171), an inhibitor of the vascular endothelial growth factor receptor, for second-line therapy of small cell lung cancer (National Cancer Institute #7097). Journal of Thoracic Oncology 2010;5:1279–84.
[146] Cabebe EC, Fisher GA, Sikic BI. A phase I trial of vandetanib combined with capecitabine, oxaliplatin and bevacizumab for the first-line treatment of metastatic colorectal cancer. Investigational New Drugs 2012;30(3):1082–7.
[147] Iwamoto H, Torimura T, Nakamura T, et al. Metronomic S-1 chemotherapy and vandetanib: an efficacious and nontoxic treatment for hepatocellular carcinoma. Neoplasia 2011;13:187–97.
[148] de Boer RH, Arrieta O, Yang CH, et al. Vandetanib plus pemetrexed for the second-line treatment of advanced non-small-cell lung cancer: a randomized, double-blind phase III trial. Journal of Clinical Oncology 2011;29:1067–74.
[149] Rizell M, Andersson M, Cahlin C, et al. Effects of the mTOR inhibitor sirolimus in patients with hepatocellular and cholangiocellular cancer. International Journal of Clinical Oncology 2008;13:66–70.
[150] Jarnagin WR, Ruo L, Little SA, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer 2003;98:1689–700.
[151] Furuse J, Okusaka T, Bridgewater J, et al. Lessons from the comparison of two randomized clinical trials using gemcitabine and cisplatin for advanced biliary tract cancer. Critical Reviews in Oncology/Hematology 2011;80:31–9.

Biographies

Donatella Marino MD received her medical degree cum laude from Messina University in 2009. Since 2010 she has been carrying out her residency in Medical Oncology at the Institute for Cancer Research and Treatment (IRCC), Candiolo, where she is part of the multidisciplinary team for the treatment of gastro-enteric malignancies. Her clinical interest involves the care of patients with pancreato-biliary malignancies.

Francesco Leone MD is the coordinator of the activities of the multidisciplinary team for the treatment of gastro-enteric malignancies at the Institute for Cancer Research and Treatment (IRCC), Candiolo. Since 2005 he has been Research Assistant at the SCDU Medical Oncology of the University of Turin, and coordinator of the translational research project between SCDU and the Oncology Laboratory of the IRCC, Candiolo. His research has mainly focused on pancreato-biliary malignancies.

Massimo Aglietta MD is a Full Professor in Medical Oncology of the University of Turin Medical School. He is Chief of the Department of Medical Oncology and Haematology at the Institute for Cancer Research and Treatment (IRCC), Candiolo. He has published over 200 papers on basic and clinical research. His main focus has been on translational research in stem cells and on their clinical application as a therapeutic strategy for the treatment of hematologic and solid malignancies.