Current state of nonsurgical therapies for cholangiocarcinoma

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Practice Points

- Cholangiocarcinomas are rare cancers with a poor prognosis.
- Curative surgery is not possible in most patients.
- Locoregional or radiation therapy can prolong overall survival in selected patients.
- Adjuvant treatment can be indicated in patients with a high risk of recurrence.
- Current standard palliative chemotherapy is the combination of gemcitabine with a platin compound.
- Molecularly targeted therapy is not yet available for clinical practice.

SUMMARY Cholangiocarcinomas (CCCs) are rare tumors that are derived from the epithelial cell lining of the bile ducts. They can be classified as intrahepatic, extrahepatic-perihilar and extrahepatic-distal tumors. The prognosis of CCCs is poor as, in many cases, they are diagnosed at advanced stages, at which point curative surgical resection is not possible. Furthermore, most patients will experience a tumor recurrence despite initial complete CCC resection. Therefore, alternative/additional therapeutic strategies are needed to improve tumor- and recurrence-free survival after surgery as well as tumor control in patients with advanced disease. In clinical practice, apart from systemic chemotherapies for the therapeutic management of CCCs, locoregional as well as multimodal strategies are available, including external and internal radiation therapies. This review focuses on the currently available nonsurgical therapies for patients with CCCs, alone or in combination with other modalities, and on evolving therapeutic concepts that are being explored in clinical studies.

Together with gall bladder cancer, cholangiocarcinomas (CCCs) belong to the biliary tract malignancies. They are derived from the epithelial cell lining of the biliary ducts. Histologically, the vast majority of CCCs are adenocarcinomas [1]. They represent a heterogenous tumor entity and can be classified, based on their localization, as intra- (IHCC) and extra-hepatic CCCs [2]. Extrahepatic CCCs can be perihilar malignancies, so-called Klatskin tumors, classified as

Bismuth–Colette tumor type I, II, IIIa, IIIb or IV [2], or distal carcinomas arising in the distal common bile duct.

CCCs are rare tumors with an estimated incidence of approximately 2/100,000 [3,4]. In the USA, mortality from CCCs has been continuously rising between 1979 and 1997 with a significant increase particularly in of IHCCs from 0.1/100,000 in 1973 to 0.7/100,000 in 1997 [5], especially in whites, blacks and Asians older than

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65 years of age [6]. Compared with the USA and western Europe, the increase in CCC incidence was significantly lower in central and northern Europe, as well as in Asia and the Middle East [7]. In Denmark, for example, between 1972 and 2002 there was a decrease in the CCC incidence from 1.2/100,000 to 0.8/100,000, both for intra- and extra-hepatic tumors [8].

Different clinical risk factors for CCC development have been identified, including biliary diseases, such as primary sclerosing cholangitis, congenital bile duct abnormalities, parasitic infections and intrahepatic gallstones, as well as viral and nonviral liver diseases, toxic agents and hereditary tumor syndromes [9].

IHCCs usually present as tumorous lesions in the liver parenchyma. Owing to their localization they are referred to as peripheral CCCs. Clinically, they are, in most cases, associated with nonspecific signs and symptoms and are usually detected in the context of the diagnostic work-up of patients complaining about fatigue and weight loss. By contrast, perihilar and distal extrahepatic tumors are, in general, identified by signs and symptoms of biliary obstruction.

The definitive diagnosis of CCC is a frequent challenge. This is particularly true for extrahepatic tumors as they are not usually accessible for histologic confirmation by percutaneous biopsy. Endoscopic intraductal tumor biopsy, including brush cytology, has a good specificity but a low sensitivity (30–60%). This may be improved by molecular analyses, such as FISH [10–13]. In the future, metabolomics may contribute to the detection of CCCs [14]. CCC diagnosis is frequently based on imaging techniques, including ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), MRI and computed tomography. The diagnostic contribution of the tumor marker CA 19–9 is limited due to its unspecific elevation in patients with biliary obstruction from any cause as well as by false-negative results in a significant number of CCC patients [15].

Therapeutic options in patients with CCCs

■ Surgery

Surgical resection is the only potentially curative treatment option. Unfortunately, only few patients are diagnosed at early enough stages or are eligible for resection. In general, liver transplantation for patients with unresectable CCC is, unfortunately, associated with poor 5-year survival rates and is, therefore, not clinical practice [16–18].

Nevertheless, for rigorously selected patients with localized, unresectable CCC after extensive staging to exclude extrahepatic spread, liver transplantation can be discussed on an individual basis. Presumably, effective neoadjuvant or adjuvant therapeutic options are required to reduce tumor recurrence in the allograft.

■ Nonsurgical interventions

Apart from systemic chemotherapy (following sections) for selected patients with unresectable but locally limited CCCs, radiation therapy, transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), or radio-frequency thermal ablation (RFA) are available with the potential for local tumor control. Furthermore, photodynamic therapy (PDT) showed promising results.

Radiation therapy

Radiation therapy can be a therapeutic option for localized CCCs in patients with tumors unresectable for technical reasons or due to a poor performance status of the patient. In CCC patients, signs and symptoms are frequently caused by cholestasis due to bile duct obstruction. In this situation, radiation therapy, possibly after initial bile duct decompression by endoscopic retrograde or percutaneous transhepatic cholangio drainage followed by stent implantation, may result in a local tumor control. External radiation therapy has been investigated alone as well as in combination with chemotherapy or intraluminal radiotherapy [19–22]. Even though local tumor progression can occur after radiation therapy, local tumor control and palliation can be achieved at least temporarily with acceptable side effects. Recent advances in radiation therapy, for example, stereotactic body radiation therapy, allow high local radiation doses to be applied to the tumor with great precision and only minimal side effects. First reports demonstrate the feasibility of this novel approach to treat localized CCCs [23,24]. Taken together, radiation therapy is, in principle, an effective therapeutic strategy for localized nonresectable CCCs. However, the optimal mode of application and the best combination regimen remains to be defined.

In patients with intrahepatic CCCs, the primary tumor arises from the biliary duct system within the liver. Furthermore, patients' prognosis is determined by local intrahepatic biliary obstruction rather than extrahepatic metastatic

disease. Therefore, locoregional treatment strategies have been evaluated in patients with CCCs, including IHCCs. In several small uncontrolled studies, the benefit of TACE with a mixture of lipiodol and a chemotherapeutic agent or with drug-eluting beads has been studied [25–30]. Tumor control has been achieved in >70% of cases. However, further clinical trials are needed to validate the utility of TACE for IHCC treatment and this is also true for SIRT. Small case series demonstrated promising response rates with a beneficial profile of side effects for IHCC [31–34]. In specialized centers, hepatic arterial infusion chemotherapy is offered as a special variant of the transarterial strategies and can be considered in selected patients.

Apart from angiographic methods, percutaneous RFA can be used to treat localized neoplasms of the liver. RFA has been shown to be beneficial for the treatment of hepatocellular carcinoma. In patients with IHCC, RFA has been evaluated in a small case series. Local tumor control could be achieved especially in small lesions <3–5 cm in diameter [35].

Taken together, in selected cases TACE, SIRT or RFA can be a useful treatment option for unresectable IHCC. In this situation, the treatment decision should be individualized and met by an interdisciplinary team.

For intraductal tumor ablation, PDT has been performed via an endoscopic retrograde or percutaneous transhepatic approach. PDT takes advantage of intravenously applicable photosensitizing drugs that accumulate in epithelial cells. After intravenous infusion of the photosensitizer, the tumor is selectively irradiated by laser light via an endoscopically or percutaneously placed optical fiber. This leads to drug activation and production of reactive oxygen species in the CCC. PDT has resulted in an impressive improvement in overall survival (OS) in two small randomized clinical trials in patients with unresectable CCC [36,37]. Conflicting with these findings, the Photostent-02 trial did not identify a significant benefit of PDT on OS [38]. A major disadvantage of PDT is the light sensitivity of patients, requiring extensive light protection for several weeks that may significantly affect patients' quality of life. An alternative to PDT could be tumor ablation by intraluminal RFA. Small preliminary studies demonstrate the feasibility of this method [39,40]. Future trials are needed to demonstrate the clinical usefulness of this approach.

Clinically, for most patients, systemic treatment strategies are options in a palliative setting or as adjuvant therapies. The decision for the optimal systemic therapeutic strategy in individual cases is, unfortunately, still based on limited data from few clinical trials and small patient numbers with this tumor entity. Here we review the current therapeutic concepts and emerging strategies for CCC patients with a focus on systemic therapies in the neoadjuvant and adjuvant, in most cases palliative setting. These, in part, combine different therapeutic principles.

Neoadjuvant therapeutic options

To date, neoadjuvant therapy is not an established option for patients with advanced CCCs. There is, however, some evidence that this approach may be beneficial in selected patients. This is based on the finding in an observational clinical series showing that three out of nine patients with extrahepatic CCCc who preoperatively received radiochemotherapy had a complete response (33%) and the other six patients had different degrees of histologic response to treatment [41]. A benefit of neoadjuvant radiochemotherapy is further suggested by a report that included 45 patients with resected extrahepatic CCC, 12 of whom received neoadjuvant radiochemotherapy [42]. Impressively, patients treated with neoadjuvant radiochemotherapy had a higher 5-year survival rate than untreated patients (53 vs 23%). Furthermore, in a recent Phase II study, the molecularly targeted therapy with the monoclonal antibody cetuximab, blocking the EGF receptor (EGFR), resulted in an objective response in 63% of patients with advanced CCC. In 30%, a downstaging that permitted a successful secondary surgical resection was achieved [43].

Adjuvant therapeutic options

■ Systemic adjuvant chemotherapy

The clinical benefit of adjuvant systemic chemotherapy after surgical CCC resection is difficult to predict due to limited evidence from randomized clinical trials. In one Phase III study from Japan, the effect of adjuvant chemotherapy with a combination of mitomycin C and 5-fluorouracil (5-FU) was analyzed in a heterogeneous group of more than 500 patients with CCC, gall bladder cancer, pancreas carcinoma or ampullary neoplasm [44]. A significant improvement in OS was only observed in the subgroup of patients with gall bladder cancer but not in the 118 CCC patients. In a recent meta-analysis

including the above-mentioned prospective study together with several retrospective studies and registry data, the effect of different adjuvant modalities was analyzed [45]. A minor benefit of adjuvant treatment including chemotherapy could be shown for patients with a high risk of CCC recurrence, for example, patients with positive lymph nodes or a R1/margin-positive resection status. However, the results from this meta-analysis need to be interpreted with caution because of the inclusion and comparison of very heterogeneous clinical patient data, different study designs and varying treatment modalities.

In the international ESPAC-3 trial, adjuvant chemotherapy with 5-FU plus folinic acid or gemcitabine was studied in 297 patients with ampullary carcinoma, 96 patients with CCC and 35 patients with other tumors [46]. Adjuvant therapy was associated with a potentially relevant prolongation of the mean OS from 35.2 to 43.1 months, however, this did not reach statistical significance. Furthermore, the subset analysis of the CCC patients showed a median survival of 27 months for untreated patients versus 18 months for patients treated with 5-FU plus folinic acid and 20 months for patients receiving gemcitabine, respectively.

In conclusion, the benefit of adjuvant chemotherapy in CCC patients remains unclear in terms of OS as well as the optimal therapeutic modality. Well-designed prospective clinical trials are therefore needed.

■ Other adjuvant therapeutic options

There are no prospective randomized trials studying the benefit of radiation therapy in CCC patients in the adjuvant setting. While several small, nonrandomized and retrospective clinical studies suggest some benefit from adjuvant radiation or radiochemotherapy [42,47–52], others do not [53,54]. It appears plausible that patients with margin-positive tumors may benefit from such modalities through an improved local tumor control. This interpretation is supported by the meta-analysis of Horgan *et al.*, despite its substantial methodical limitations [45]. Again, for the demonstration of a benefit from radiation or radiochemotherapy in CCC patients, well-designed prospective clinical trials are needed.

Palliative therapeutic options

■ Chemotherapy

Numerous trials have demonstrated the benefit of palliative chemotherapy for patients with

advanced CCCs (Table 1). The most extensively studied drugs are 5-FU plus folinic acid and gemcitabine with response rates for monotherapy in the range of 10–30%. Furthermore, the combination of different drugs turned out to be superior compared with monotherapy. Among different cytotoxic drugs, the combination of a platinum compound with gemcitabine appeared to be most beneficial in a meta-analysis of 104 small trials [55]. The superiority of this combination therapy could also be shown in several prospective Phase III trials. In the study by Sharma *et al.*, patients with unresectable gall bladder cancer were randomized into three arms: best supportive care; 5-FU plus folinic acid; and a modified combination of gemcitabine and oxaliplatin (GEMOX) protocol [56]. GEMOX therapy resulted in a significant improvement in OS from 4.5 to 9.5 months. In the largest Phase III trial (ABC-02 study) 410 patients with locally advanced or metastatic CCC, gall bladder cancer, or ampullary cancer were treated with gemcitabine alone or gemcitabine combined with cisplatin [57]. The combination therapy significantly increased median OS from 8.1 to 11.7 months, median progression-free survival from 5.0 to 8.0 months and tumor control from 71.8 to 81.4%. However, neutropenia was more frequent in patients receiving gemcitabine plus cisplatin without significant differences in the rate of neutropenia-associated infections. Comparable results were obtained in a similar smaller Phase II trial from Japan including 83 patients with advanced biliary tract cancer: the addition of cisplatin prolonged OS from 7.7 to 11.2 months [58].

In conclusion, the combination of gemcitabine and cisplatin can be considered the standard treatment of advanced nonresectable CCCs and is well tolerated.

In addition to the combination of gemcitabine and cisplatin, other gemcitabine combination therapies have been explored but not directly compared with gemcitabine and cisplatin. Examples include capecitabine, irinotecan and oxaliplatin [59–61]. While the meta-analysis mentioned above concluded that the combination of gemcitabine with a platinum compound results in the highest objective response and tumor control, it did not translate into a significant benefit in terms of time to tumor progression or median OS [55]. In view of these limitations, gemcitabine and cisplatin is, at present, the standard therapeutic option for patients with advanced CCC.

Table 1. List of clinical trials evaluating chemotherapeutic agents and targeted therapies in patients with unresectable biliary tract cancer.

Study (year)	Regimen	Patients (n)	Localization	Disease control rate (CR, PR and SD, %)	Median PFS (months)	Median OS (months)	Ref.
Sharma <i>et al.</i> (2010)	BSC versus	27	GBC	4	2.8	4.5	[56]
	FUFA versus	28		21	3.5	4.6	
	GEMOX	26		69	8.5	9.5	
Valle <i>et al.</i> (2010)	Gem versus	206	CCC, GBC and AC	71.8	5.0	8.1	[57]
	Gem/cis	204		81.4	8.0	11.7	
Okusaka <i>et al.</i> (2010)	Gem versus	42	CCC, GBC and AC	50.0	3.7	7.7	[58]
	Gem/cis	41		68.3	5.8	11.2	
Koeberle <i>et al.</i> (2008)	Gem/cap	44	CCC and GBC	80	7.2	13.2	[59]
Andre <i>et al.</i> (2004)	GEMOX	33	CCC, GBC and AC	61	5.7	15.4	[61]
Philip <i>et al.</i> (2006)	Erlotinib [†]	42	CCC and GBC	50	2.6	7.5	[63]
Lubner <i>et al.</i> (2010)	Bevacizumab plus erlotinib	49	CCC and GBC	63	4.4	9.9	[64]
Gruenberger <i>et al.</i> (2010)	GEMOX plus cetuximab	30	CCC and GBC	80	8.8	15.2	[43]
Lee <i>et al.</i> (2012)	GEMOX versus	133	CCC, GBC and AC	67	4.2	9.5	[65]
	GEMOX plus erlotinib	135		66	5.8	9.5	

[†]57% of the patients were pretreated.

AC: Ampullary carcinoma; BSC: Best supportive care; cap: Capecitabine; CCC: Cholangiocarcinoma; cis: Cisplatin; CR: Complete remission; FUFA: 5-fluorouracil plus folinic acid; GBC: Gall bladder cancer; Gem: Gemcitabine; GEMOX: Gemcitabine and oxaliplatin; OS: Overall survival; PFS: Progression-free survival; PR: Partial remission; SD: Stable disease.

It remains unclear whether a second- or third-line therapy offers a clinically relevant benefit. It is most likely that the patients' reduced performance statuses do not allow a cytostatic therapy in many patients in this situation, as shown by a recent retrospective single-center analysis of 395 patients [62]. Only 25% of the patients received a second-line and 6% a third-line treatment that resulted in a response in 9% and a stable disease in 34% of patients.

Molecularly targeted therapies

Significant advances have been achieved in the treatment of solid tumors with targeted therapies during the last few years. This treatment strategy was also evaluated in clinical trials including patients with CCCs.

The oral tyrosine kinase inhibitor erlotinib that interferes with the EGFR pathway was evaluated as monotherapy in 42 patients with advanced CCC, 57% of whom had received prior chemotherapy [63]. Among these patients there were only three (7%) showing a partial response while seven additional patients had progression-free survival at 6 months (16%). Furthermore, in a study including 53 patients with advanced CCC and ten patients with gall bladder cancer, daily oral erlotinib was evaluated in combination with the biweekly administration of the monoclonal antibody bevacizumab, which targets the VEGF [64]. Six patients (12%)

achieved a partial response beyond 4 weeks and 51% had a stable disease. Whether this biologic-only combination is better than the conventional cytotoxic therapy requires further evaluation.

The combination of erlotinib with GEMOX was evaluated in 268 South Korean patients with biliary tract cancer, including intra- and extra-hepatic CCCs, gall bladder cancers and tumors of the ampulla Vateri [65]. While the objective response rate was 30% in the combination group compared with 16% in the GEMOX-only group, there was no significant difference in overall survival. Whether there is a correlation between the response to erlotinib and a mutation of the *EGFR* gene, as shown for the advanced non-small-cell lung cancer, requires further analysis.

In another Phase II study, the monoclonal antibody cetuximab, targeting the EGFR, was evaluated in 30 patients with nonresectable advanced or metastatic biliary tract cancer in combination with GEMOX [43]. An objective response was achieved in 19 patients (63%), three of whom (10%) had a complete response and nine patients (30%) a downstaging that allowed a secondary surgical resection. These results are promising, even though long-term outcomes and controlled data are pending.

The interim results from a similar prospective, randomized study (BINGO trial), evaluating the efficacy of GEMOX with and without cetuximab, also suggest an improvement in

progression-free survival [66]. Final results from this study may allow a better assessment of the benefit of this treatment strategy.

Other targeted therapies in combination with cytotoxic agents have been studied in small clinical trials of patients with advanced CCCs. These targeted therapies included bevacizumab [67] and the multikinase inhibitor sorafenib [68].

Taken together, the results from clinical studies carried out to date provide no clear evidence that molecularly targeted therapies alone or in combination with chemotherapeutic strategies should be used in clinical practice for patients with advanced CCCs. Larger, randomized controlled studies are necessary to determine their therapeutic benefit for these patients.

Conclusion & future perspective

CCCs are rare malignancies derived from biliary epithelial cells with a poor prognosis. At diagnosis, most tumors are at too advanced stages for surgical resection, which is the only curative treatment option. Even after complete R0/margin-free resection, relapse rates are high and most patients will eventually require palliative treatment. The impact of adjuvant therapy is still not clearly defined. Cytostatic chemotherapy

combining gemcitabine with a platinum compound is, at present, standard treatment of advanced CCCs. Targeted treatment strategies have not yet entered clinical practice. In selected/individual patients, radiation, radiochemotherapy, RFA, TACE, SIRT or PDT can be discussed as therapeutic options. Unfortunately, most palliative treatment strategies are based on very limited evidence from clinical studies due to the low incidence of CCCs. Therefore, data from randomized prospective clinical trials enrolling a larger number of patients are urgently needed. CCC patients should be discussed in interdisciplinary tumor boards and, if possible, included in randomized, controlled clinical trials.

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.

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