Current State of Multidisciplinary Treatment in Cholangiocarcinoma

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Keywords

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to ensure optimal patient care at specialized centers. Molecular profiling of patients and inclusion into clinical trials is highly recommended.

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Abstract

Background: Cholangiocarcinoma (CCA) is a highly aggressive malignancy, and its incidence seems to be increasing over the last years. Given the high rate of irresectability at the time of initial diagnosis, new treatment approaches are important to achieve better patient outcomes. Our review provides an overview of current multimodal therapy options across different specialties of gastroenterology/oncology, surgery, and interventional radiology. **Summary:** CCA is subdivided into clinically and molecularly distinct phenotypes. Surgical treatment currently is the only potentially curative therapy, but unfortunately, the majority of all patients are not eligible for resection at the time of initial diagnosis due to anatomic location, inadequate hepatic reserve, metastatic disease, or limiting comorbidities. However, multimodal treatment options are available to prolong survival, relieve symptoms, and maintain life quality. **Key Messages:** The treatment of CCA is complex and requires close interdisciplinary collaboration and individualized treatment planning

Introduction

Cholangiocarcinoma (CCA) is a highly aggressive, heterogenous malignancy originating from the epithelium of the biliary tract. CCA is considered a relatively rare cancer accounting for <1% of all human cancers and the second most common primary liver cancer after hepatocellular carcinoma [1]. A varying distribution of risk factors and genetic susceptibility results in a high variability in CCA incidence [2]. While in the USA and Europe 1.6–3.4 cases per 100,000 inhabitants occur [3], South East Asia reports up to fiftyfold higher incidence rates, mainly due to endemic liver fluke infections (i.e., *Clonorchis sinensis* or *Opisthorchis viverrini*) [4]. CCA is slightly more common in men with a median age of onset between 60 and 70 years [5]. Most cases of CCA are sporadic. However, well-known risk factors were identified and are largely based on chronic biliary obstruction (e.g., due to

Fig. 1. Classifications of CCA. CCA arise from the epithelium of the biliary ducts within healthy or diseased liver parenchyma (e.g., cirrhosis, PSC, and chronic viral hepatitis). CCA are anatomically subclassified into CCA, pCCA, and distal CCA (dCCA). pCCA and dCCA are collectively referred to as extrahepatic CCA (eCCA). Intrahepatic CCA most typically shows mass-forming growth but can also present as periductal-infiltrating or intraductal-growing tumor. Perihilar CCA are subdivided according to the Bismuth-Corlette classification and can grow in the common hepatic duct below the confluence (type I), reach the hepatic duct confluence (type II), involve common hepatic duct and the right (type IIIa) or left (type IIIb) hepatic duct or both right and left hepatic duct up to segmental infiltration (type IV, not shown). dCCA arise distal from the insertion of the cystic duct in the common bile duct. CCA, cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar CCA; dCCA, distal CCA.

primary sclerosing cholangitis, gall stones, and biliary cysts), inflammation and lifestyle aspects [6, 7]. Liver fluke infections, chronic viral hepatitis, nonalcoholic fatty liver disease, and cirrhosis are accompanied by prolonged inflammation of the bile ducts and thereby predispose to CCA development [8–10]. Furthermore, lifestyle aspects such as cigarette smoking, alcohol drinking, and obesity as well as type 2 diabetes and hypertension are associated with increased CCA risk [11, 12].

Anatomically and clinically, CCA is divided into 3 subgroups (Fig. 1) [13]:

1. Intrahepatic CCA (iCCA) arising from the segmental branches of the bile ducts.
2. Perihilar CCA (pCCA), historically called “Klatskin tumors,” involving the right, left, and/or main hepatic duct as further subclassified by Bismuth-Corlette based on the ductal extent [14, 15].
3. Distal CCA (dCCA) growing in the common bile duct distal from the insertion of the cystic duct.

iCCA accounts for 5–10% of biliary tract cancers [13, 16]. However, iCCA incidence and mortality increased globally in the last decade probably due to a rise in major risk factors (viral hepatitis, obesity) and improvements in diagnosis which render misclassification of iCCA as cancer of unknown primary in the liver less common [1]. pCCA and dCCA constitute the majority of tumors (60–70% and 20–30%, respectively), but their incidence tends

to decline [17–19]. However, reports on the epidemiology of CCA should be valued with caution due to the changing nomenclature of the International Classification of Diseases (ICD) editions [18, 20]. Based on its growth pattern, CCA can also be categorized into the mass-forming type appearing as nodular lesions in the liver parenchyma, the periductal-infiltrating type growing along the biliary tree and the rare intraductal-growing type [21, 22]. The anatomical localization of the different subtypes determines their clinical appearance. iCCA is frequently asymptomatic in earlier disease stages and only apparent as incidental finding on imaging or in advanced stages with clinical symptoms such as abdominal pain, weight loss, nausea, and jaundice [13, 23, 24]. pCCA and dCCA typically present with jaundice due to obstruction of biliary tracts in 90% of cases, occasionally complicated by cholangitis [13]. 70% of CCA are diagnosed in advanced disease stages as defined by tumor invasion into the peritoneum and adjacent organs or extrahepatic spread [25]. The diagnosis of CCA is based on multimodality imaging such as computed tomography and magnetic resonance imaging. Because no specific radiological pattern is established for CCA, confirmatory histology from percutaneous/cholangioscopy-guided biopsy or endoscopic retrograde cholangiopancreatography (ERCP) is mandatory.

Color version available online

Fig. 2. Treatment flowchart for patients with CCA. BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group Performance Status; FOLFOX, folinic acid, 5-fluorouracil and oxaliplatin; Gem/Cis, gemcitabine and cisplatin; HDR-BT, high-dose-rate brachytherapy; mo, months; mOS, median overall survival; MWA, microwave ablation; RE, yttrium-90 radioembolization; RFA, radiofrequency ablation; TACE, transarterial

chemoembolization; yr, years; CCA, cholangiocarcinoma. *Pemigatinib, entrectinib, larotrectinib, ivosidenib and pembrolizumab are approved by the FDA for treatment of patients with the respective genetic markers. *Biopsy and molecular profiling are recommended by the NCCN in patients with unresectable CCA, after liver transplantation has been ruled out as therapeutic option.

Treatment

Surgical Resection and Liver Transplantation

Surgical resection is the only potential curative therapeutic approach in CCA [26]. The main objectives of surgery are tumor-free resection margins (R0), locoregional lymphadenectomy, and a sufficient future liver remnant (FLR). However, the majority of patients present with late-stage disease determining palliative treatment (Fig. 2).

The therapeutic strategy varies distinctly between iCCA, pCCA, and dCCA depending on the tumor location along the biliary tract. Thus, a precise preoperative diagnostic workup is highly demanded. Required diagnostic modalities include a CT scan with an arterial and a venous phase, a MR scan with liver-specific contrast agents and for pCCA and dCCA an ERCP. If preoperative biliary drainage is necessary, particularly the FLR has to be drained. Biliary drainage aims to increase possible FLR hypertrophy and reduce postoperative morbidity and mortality [27–29]. In the case of pCCA or dCCA, a biliary drainage should not be inserted before the diagnosis has

been secured since local inflammation might hinder the diagnosis [30]. However, the preferred drainage technique is still a matter of debate internationally. A multicenter, randomized controlled trial, comparing endoscopic versus percutaneous biliary drainage, had to be prematurely terminated due to increased mortality rates in the percutaneous transhepatic biliary drainage group [31]. Nonetheless, the percutaneous approach, which requires a high expertise and might lead to bleeding, has advantages as well (lower rates of infections and recurrent obstructions) [30, 32, 33]. The endoscopic insertion of a stent or a naso-biliary drainage, in turn, is associated with lower rates of bleeding, but with higher rates of infectious complications, such as cholangitis, pancreatitis, or surgical side infections [31, 34]. An internal drainage increases patient comfort compared to either a naso-biliary or a percutaneous drainage.

Among surgically treated CCA, 10% are intrahepatic [35]. These tumors are often multifocal; thus, MR imaging is essential to detect (micro-)metastases. An imaging-based volumetric approximation of the FLR or additional liver function tests [36, 37] helps to avoid post-hepatec-

tomy liver failure. If an insufficient FLR is expected, hypertrophy has to be achieved. To attain hypertrophy of the FLR a 2-step approach, including either portal vein embolization (PVE), in situ split (ALPPS), portal vein ligation (PVL), or interventional approaches, has to be evaluated on an individual basis [38–41]. Although the rates of FLR hypertrophy are similar between PVE and PVL, interventional procedures are preferred to induce hypertrophy of the FLR because they are less invasive [42]. In recent years, the effect of PVE has been evaluated in healthy livers as well as in pathologic livers, such as fibrosis or cirrhosis. Induction of hypertrophy is usually tested after 4–6 weeks and a hypertrophy of approximately 40% is expected in healthy livers [42, 43]. A further development of PVE is liver venous deprivation technique. This approach combines a PVE with the interventional occlusion of the right hepatic vein. It seems that this new technique achieves comparable results regarding time and hypertrophy compared to the “Associating Liver Partition and Portal vein Ligation for Staged hepatectomy” (ALPPS) procedure [44, 45]. Furthermore, radioembolization, another interventional approach, combines the induction of hypertrophy of the FLR with a direct treatment of the hepatic tumor burden. Thus, this approach might prevent patients from not being considered for surgery due to hepatic tumor progression [40, 46, 47].

Resection of pCCA is guided by the Bismuth-Corlette [14] classification (Fig. 1). Due to the close proximity of the main bile duct, the portal vein and the hepatic artery, CT imaging, including arterial and venous phases, is crucial to assess vascular involvement. MRI and MRCP are most suitable to detect the main tumor. In case of intrahepatic cholestasis or cholangitis due to tumor obstruction, preoperative ERCP or percutaneous transhepatic cholangiography drainage might be necessary to reduce pressure in the FLR and decrease postoperative complication rates [48]. In cases of type I pCCA, the resection might be limited to the bile duct confluence [35]. However, also type I tumors often require an (extended) hemihepatectomy including the caudate lobe. Since the left main bile duct is longer than the right main bile duct, commonly a right-sided liver resection is performed. This approach leads to a greater chance of achieving tumor-free resection margins and facilitates the complete removal of the tumor mass preventing accidental tumor opening (no-touch technique). The same operative strategy might be feasible for type II and IIIa pCCA. A partial resection of the portal vein might additionally be necessary [49]. On the other hand, type IIIb pCCA requires a left-sided hemihepatectomy. From a surgical point of

view, this scenario is probably the most challenging because the bile duct reconstruction includes 2–4 segmental branches and the resection of the caudate lobe. Second, an appropriate venous drainage of the remaining part of the right lobe has to be ensured while obligatorily resecting the middle liver vein. However, even in highly specialized centers, morbidity and mortality are high. Postoperative liver failure is thereby a feared complication [50]. Patients with CCA undergoing major resections have the highest complication rates as compared to other liver malignancies, but specialized centers feature with significantly lower complication rates [51, 52].

Liver transplantation might be considered in very few selected cases of iCCA and pCCA. The evidence for liver transplantation is weak and based on few case series, mostly retrospective [53–56]. A retrospective, multicenter study by 12 US transplantation centers published convincing data for selection criteria and neoadjuvant therapy of pCCA patients [55]. However, transplantation should only be done as part of clinical studies and if complete resection is not possible either due to inclusion of the distal hepatic artery or lack of bile duct remnants for anastomoses. Moreover, it seems that tumor biology is a more robust factor regarding eligibility for transplantation than tumor size. Thus, stable disease of at least 6 months is required prior liver transplantation [53]. Eligibility criteria are strict and extrahepatic tumor masses after neoadjuvant radio-chemotherapy have to be ruled out [57].

Surgery for dCCA commonly requires a pancreaticoduodenectomy and the main challenge is to attain tumor-free resection margins at the proximal bile duct. Extended multivisceral resections, including liver or colon, are only feasible in highly selected patients [58].

Adjuvant and Neoadjuvant Therapy

Curative resection aims at long-term disease-free survival. Due to the frequent relapse of CCA after surgery, there is an urgent need for effective adjuvant treatment. CCA relapse after curative surgery occurs globally in around 67–73% of patients with a median time to recurrence of 11–14 months [59–61] (Fig. 2). Unfortunately, only a small proportion of patients are amenable to repeated resection with curative intent after recurrence [61, 62]. The Bile Duct Cancer Adjuvant Trial and the PRODIGE-12-ACCORD-18 study failed to show a benefit for adjuvant gemcitabine and combination therapy with gemcitabine and oxaliplatin, respectively [63, 64]. In the BILCAP trial, adjuvant capecitabine significantly prolonged disease-free survival across all biliary cancer subtypes, while no significance in overall survival (OS) was

observed in the intention to treat population (51 vs. 36 months; $p = 0.097$). However, as data from a per-protocol analysis (51 vs. 36 months; $p = 0.028$) demonstrated a significant survival benefit adjuvant capecitabine is now considered standard of care [65, 66].

Results of 2 phase III trials are highly anticipated. The ongoing ACTICCA-1 study, investigating the role of gemcitabine and cisplatin, has been delayed in completion due to protocol adaptations to account for the change in clinical standard from observation to capecitabine treatment [67]. The ASCOT trial evaluating the effect of adjuvant S1, a modulated oral fluoropyrimidine prodrug, has finished recruiting recently; results have not been published to date [68]. Among a growing number of phase II trials, one of the most notable is the SWOG-0809 trial, which reported a promising 2-year survival rate of 65% after adjuvant radiotherapy in combination with gemcitabine and capecitabine in patients with eCCA or gallbladder cancer presenting with high-risk features [69]. Most recent approaches explore combination therapies with capecitabine including radiotherapy, tyrosine kinase inhibitors, and immune checkpoint inhibitors (CPI). It remains unclear if the promising results for molecular targeted therapies described below can be transferred into the adjuvant setting as well.

At the moment, there is no role for neoadjuvant treatment for CCA. Some phase I and II trials have been performed, enrolling low patient numbers. The GAIN trial investigating the efficacy of neoadjuvant and adjuvant gemcitabine/cisplatin is the first randomized clinical trial (RCT) in resectable biliary tract cancer [70]. Results are expected by 2024.

Locoregional Treatment

For patients with unresectable iCCA as well as intrahepatic CCA metastases, various locoregional therapy options exist in addition to systemic therapy [71]. Up to now the evidence is not strong with most of the conclusions drawn from single-center retrospective analyses with small sample sizes treated in the salvage situation. However, the results are promising and suggest a survival benefit in the treatment of unresectable CCA in selected patients, even in an advanced stage with extrahepatic disease. Moreover, leading goals of palliative locoregional therapy are to control local tumor growth, relieve symptoms, and improve and maintain quality of life. In a curative setting, preoperative PVE as an interventional procedure enables patients with too little standardized FLR to achieve resectability by inducing hypertrophy of the healthy liver.

Local Ablative Techniques

Local ablative procedures such as radiofrequency ablation (RFA), microwave ablation (MWA), or interstitial high-dose-rate brachytherapy (HDR-BT) can be used in patients with circumscribed single or few intrahepatic lesions. As ablative techniques, their intention is complete and durable local tumor destruction. Nevertheless, there are limitations in the use of thermal methods (RFA and MWA) depending on the size and location of the tumors. Adjacent large blood vessels cause cooling effects that may counteract adequate heat generation and hinder complete ablation of the tumor [72]. Peripheral lesions adjacent to hollow organs, as well as centrally located lesions (near or comprising the major bile ducts), are only partially amenable to thermal-based ablation due to associated complications. Regarding size limitation, the German Society for Interventional Radiology and Minimally Invasive Therapy (DEGIR) recommends a maximum tumor diameter of 3.5 cm for multifocal metastasis and 5 cm for a single focus to ensure safe ablation. Considering that iCCA is usually diagnosed in an advanced stage, these restrictions usually preclude the application of thermal methods and they therefore play a minor role in the therapy regime. However, small tumors as first diagnosis or as recurrence in the remnant liver after initial surgery in patients not willing or eligible for (re)resection, could be candidates for thermal ablation. For example, a small single-center study with 13 patients described a local control rate of 88% and a median OS of 38.5 months in selected patients with small lesions (<5 cm) after thermal ablation [73].

In contrast, image-guided interstitial brachytherapy (HDR-BT, a catheter-based radiotherapy) is largely independent of tumor location and tumor size, and thus can be used for larger tumors, as well as for lesions in proximity to hilar structures. In brief, liver tumors are treated with a high-dose rate iridium-192 source in afterloading technique after percutaneous positioning of brachytherapy catheters under CT or MRI control [74–78]. The prescribed minimum dose for the clinical target volume is 20 Gy [79, 80]. Specifically, in patients where RFA or MWA is not feasible, HDR-BT is a useful option in selected patients. Schnapauff et al. [77] evaluated outcomes after repeated HDR-BT in 15 therapy-naïve patients (27 sessions) with unresectable iCCA who suffered from limited hepatic disease only (<5 lesions, size up to 12 cm), revealing a median survival of 14 months after HDR-BT and 21 months after primary diagnosis. Further on, effective treatment with HDR-BT of iCCA recurrences after initial resection was shown with a 1-year and 5-year survival of

77.1% and 51.4%, respectively, in a small case series of 10 patients [81]. Data on combined local treatment and chemotherapy is not published yet. However, there are recruiting trials evaluating the efficacy of HDR-BT in combination with gemcitabine and cisplatin in irresectable iCCA patients (CHOICE trial, DRKS00007161).

Locoregional Therapies

For patients with multifocal or diffuse hepatic involvement, locoregional therapeutic procedures, such as transarterial chemoembolization (conventional TACE or TACE with drug eluting beads), or yttrium-90-radioembolization (RE) are available if liver function is sufficient [82–84]. Several retrospective cohorts were published analyzing the outcome after TACE in iCCA patients. OS ranged from 10 to 16.3 months, reported objective response rate (RR) usually did not exceed 25% [83, 85–92]. Comparing objective response, OS, and tolerability, RE seems to be superior to TACE [93]. Multiple retrospective studies analyzed outcome after RE in unresectable iCCA patients who were treated in different settings: therapy-naïve, as intensification during chemotherapy, and in chemotherapy-refractory stage [71, 82, 84, 94–102]. A meta-analysis of 298 patients reported a pooled median OS of 14.3 months after RE [103], indicating superior survival compared to chemotherapy with gemcitabine and cisplatin alone (11.7 months) [104]. However, studies contained mixed populations and a selection bias needs to be assumed. Furthermore, a recent post hoc analysis of prospective trials showed that patients diagnosed with advanced iCCA have a better OS (16.7 months) compared with other biliary tract cancers after first-line chemotherapy with gemcitabine and cisplatin, which indicates that survival data from Valle et al. [105] are underestimated with respect to this patient subgroup that is predominantly accessible for radiological interventional therapies. These results were confirmed in a prospective trial combining RE and gemcitabine/cisplatin, with a median progression-free survival (PFS) of 30% at 24 months, and 22% of patients downstaged to resection. Out of these, median relapse-free-survival was not reached at 46 months [106]. Results have been used to prepare an upcoming phase 3 study design (NCT02807181).

Further studies which included the combination of RE and chemotherapy with gemcitabine and cisplatin indicated superior efficacy of combined treatment compared with RE alone [82], others suggested similar efficacy [107]. Importantly no study suggests increased toxicity when the treatments were combined.

The fact that patients usually present for such procedures only at an advanced and often chemotherapy-refractory stage of disease is important for the interpretation of the published data. Considering this, survival rates with a survival time of 10–18 months after locoregional therapy are relatively high [108]. The efficacy of RE and TACE is further underlined by reports of secondary resectability after treatment (although in rare and individual cases only) [109] as well as high local RRs, which are probably a better descriptor of efficacy here, as many patients receive further systemic therapies before and often after local treatment, and thus survival results reflect combinations of different therapies, or different therapy timing. Interestingly, many studies observed that the presence of limited extrahepatic manifestations (usually lymph nodes, bone, and lung) had no impact on survival indicating that local tumor control and concomitant maintenance of liver function is essential for outcome [71, 93].

Altogether, studies on interventional radiologic therapies for iCCA show encouraging results in selected patients regarding OS, so that these treatment options are gaining increasing attention, also considering the limited options for systemic therapy. Such therapeutic approaches might be used in individualized treatment concepts, but data need validation in larger prospective trials. Encouragingly, the efficacy of RE as combination therapy with gemcitabine/cisplatin versus gemcitabine/cisplatin alone in the first-line setting is currently being investigated in a large prospective multicenter study (NCT02807181).

Endoscopic Therapies

In addition to the supportive role of endoscopy to treat biliary tract or GI-tract obstruction and cholangitis in CCA, endoscopic intraluminal ablative approaches such as photodynamic therapy (PDT) or RFA have also been investigated. Several retrospective studies, 2 small RCTs and a meta-analysis demonstrated a promising benefit for PDT in patients with unresectable biliary tract cancer [110–112], while a recent large randomized study in patients with locally advanced or metastatic disease showed an inferior survival for patients treated with PDT [113]. RFA is another intraductal ablative procedure with promising data in clinical studies. Recent data from a systematic meta-analysis [114] and 2 RCTs [115, 116] comparing biliary RFA and stenting versus stenting alone demonstrated a survival benefit and manageable safety profile of intraductal RFA. Based on the limited data, both approaches can be considered as palliative treatment op-

tions in patients with unresectable perihilar or dCCA and cholestasis, although PDT is not widely used. Clinical studies directly comparing the efficacy of PDT and RFA are lacking. Furthermore, a possible role of intraluminal approaches in combination with systemic chemotherapy remains to be elucidated. Yang and colleagues [117] recently reported a RCT showing favorable efficacy and safety for RFA combined with chemotherapy with the agent S1 as combined to RFA alone for unresectable eCCA. An ongoing RCT examines the benefit of combined PDT and systemic chemotherapy with gemcitabine/cisplatin (NCT04099888).

Systemic Treatment for Advanced CCA

Systemic treatment is the mainstay of therapy in patients with unresectable CCA. The aim of systemic therapy is to prolong patient's survival and to reduce cancer-associated symptoms while maintaining a sufficient quality of life and minimize treatment-associated toxicity. Patients with bad performance status, as defined by an Eastern Cooperative Oncology Group (ECOG) performance status >2 or impaired liver function disqualify for systemic treatment.

Cytotoxic Chemotherapy

More than a decade after the publication of the ABC-02 trial and the confirmatory Japanese BT22 study [118, 119], Gemcitabine/cisplatin remains the globally accepted standard of care in the first-line treatment of advanced CCA. Gemcitabine/cisplatin markedly improved the primary endpoint of OS as compared to gemcitabine alone, with a median OS of 11.7 months versus 8.1 months ($p < 0.001$), a median PFS of 8.0 months versus 5.0 months ($p < 0.001$), and a RR of 26.1% versus 15.5% [119]. Gemcitabine/cisplatin reduces the rate of cholangitis and liver failure [120]. Upon progression on first-line chemotherapy, the ABC-06 trial established mFOLFOX (modified FOLFOX, consisting of folinic acid, 5-fluorouracil, and oxaliplatin) as second-line treatment based on a small, but statistically significant difference in median OS with 6.2 months for mFOLFOX versus 5.3 months with active symptom control ($p = 0.031$) and a clinical meaningful benefit in 6- and 12-months survival rates (50.6% vs. 35.5%, 25.9% vs. 11.4%) [121]. Median PFS was 4.0 months and RR 5%. The benefit of mFOLFOX was consistent among all subgroups and even in patients resistant or refractory to platinum in the first line.

Newer studies focus on triple agent combinations to further increase antitumor activity. The addition of nab-paclitaxel to gemcitabine/cisplatin in a phase II trial dem-

onstrated an impressive median OS of 19.2 months, a PFS of 11.8 months, and an overall RR (ORR) of 45% with some patients downstaged to resectability [122]. Based on these findings, a phase III trial is comparing the combination of nab-paclitaxel/gemcitabine/cisplatin to the standard of care gemcitabine/cisplatin (NCT03768414). A Japanese trial showed a significant improvement of survival and PFS with the agent S1 and gemcitabine/cisplatin as compared to gemcitabine/cisplatin alone (OS 13.5 months vs. 12.6 months; $p = 0.046$, PFS 7.4 months vs. 5.5 months; $p = 0.0015$). The first-in-class compound NUC-1031 is a prodrug of gemcitabine and was developed to overcome major resistance mechanisms to gemcitabine [123]. Based on favorable results in the CCA cohort in a phase I basket trial, the combination of NUC-1031 and cisplatin in comparison to gemcitabine/cisplatin is currently being investigated in a phase III trial (NCT04163900). FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin), highly active in patients with metastatic pancreatic cancer [124], failed to show a clinical benefit in biliary tract cancer in a French phase II/III trial [125].

Molecularly Targeted Therapy

CCA is a genetically complex tumor with a high number of mutations affecting various oncogenic pathways [126–129]. The current development of CCA therapy is an outstanding example of precision medicine, with next-generation sequencing approaches identifying actionable mutations across the different disease subtypes and circulating tumor DNA used to monitor treatment response and emergence of resistant clones as part of biomarker-based clinical trials [130] (Table 1). More than 50% of patients with intrahepatic CCA show targetable mutations, as reviewed by Lamarca and colleagues [131]. Briefly, the most common involve fibroblast growth factor receptor 2 (FGFR2) gene fusions and isocitrate dehydrogenase (IDH) 1 and 2 mutations (each in around 20% of cases), less common B-raf kinase (BRAF) mutations, ERBB alterations, or tropomyosin receptor kinase (TRK) fusions [129, 132, 133]. In contrast, the molecular profile of eCCA shows similarity to pancreatic ductal adenocarcinoma with frequent mutations in KRAS, TP53, SMAD4, and ERBB family.

FGFR gene alterations have been identified as driver mutations in intrahepatic cholangiocarcinogenesis with FGFR2 gene fusions being the most prevalent and the most sensitive to FGFR inhibition [134]. Various reversible (infigratinib, pemigatinib, derazantinib, and erdafitinib) and irreversible (futibatinib) selective, oral FGFR-inhibitors have been developed and investigated as

Table 1. Targeted agents for treatment of advanced CCA

Biomarker/ target	Prevalence, %	Drugs	Trial phase	Patients, <i>n</i>	ORR, %	PFS, mo	OS, mo	Side effects (pooled)	Refer- ences
FGFR	iCCA: 20+ eCCA: 3+	Infigratinib	2	108 (108°)	23.1	7.3	12.5	Hyperphosphatemia, fatigue, stomatitis, diarrhea, alopecia, eye toxicity	[115, 120]
		Pemigatinib	2	146 (107°)	35.5*	6.9*	21.1*		[116]
		Derazantinib	1/2	29 (29°)	20.7	5.7	NR		[118]
		Erdafitinib	2a	14 (8°)	50.0	5.6	NR		[119]
		Futibatinib	2	103 (103°)	37.3	7.2	NR		[121, 122]
IDH	iCCA: 20+ eCCA: 3+	Ivosidenib	3	187	2	2.7	10.3	Nausea, diarrhea, abdominal pain, fatigue, ascites	[124]
TRK	4+	Entrectinib	2	54 (1#)	57	11.2	21	Weight gain, transaminitis, anemia, dizziness, fatigue	[134]
		Larotrectinib	2	55 (2#)	75	NR	NR		[133]
BRAF ^{V600E}	3+	Dabrafenib/ trametinib	2	43	47	NR	NR	Increased GGT, pyrexia, nausea, vomiting, diarrhea	[135]
MSI-H	1–5	Pembrolizumab	2	22	40.9	4.2	24.3	Fatigue, pruritus, diarrhea, irAEs	[145]

BRAFV600E, B-raf kinase V600E mutation; FGFR2, fibroblast growth factor receptor 2 alterations; GGT, gamma-glutamyl transferase; IDH1, isocitrate dehydrogenase 1; irAEs, immune-related adverse events; mo, months; MSI-H, high microsatellite instability; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase fusions; CCA, cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma.

* Adapted from [131]. * Pemigatinib results for cohort 1, patients with FGFR2 gene alterations. ° Number of patients with FGFR2 fusions/rearrangements.

Number of patients with CCA in the study population of patients with TRK positive cancers.

monotherapy in phase 2 trials in pretreated patients with advanced iCCA (Table 1). Outcomes in patients with FGFR2 gene fusions were impressive: ORR ranges from 21% to 50% with high disease control rates of 82–84%, median PFS of 5.9–7.3 months, and OS of 12.5–21.1 months [135–139]. However, in patients without FGFR alterations, these agents did not show activity. Side effects are similar and include hyperphosphatemia due to inhibition of FGF-mediated phosphate elimination in the kidneys, fatigue, gastrointestinal (stomatitis and diarrhea); skin (alopecia and nail changes); and eye (dry eye, conjunctivitis, and vision changes) toxicity. With pemigatinib the first FGFR-inhibitor has been approved by the FDA for the treatment of patients with advanced iCCA and FGFR2 gene fusions in April 2020 [137], infigratinib is currently being reviewed by the FDA for the same indication [140]. Three randomized phase III trials evaluate the efficacy of infigratinib (NCT03773302), pemigatinib (NCT03656536), and futibatinib (NCT04093362) against gemcitabine/cisplatin in the first-line treatment of advanced iCCA with FGFR2 gene alterations.

Mutations in IDH 1/2 enzymes lead to the production of the oncometabolite 2-hydroxyglutarate stimulating DNA-hypermethylation leading to CCA formation and progression [133]. The phase III ClarIDHy study ran-

domized pretreated patients with advanced, IDH1 mutant CCA to receive either the IDH1 inhibitor ivosidenib or placebo with primary endpoint PFS and the possibility for cross-over after progression (Table 1). Ivosidenib improved the primary endpoint with a median PFS of 2.7 months versus 1.4 months ($p < 0.0001$), but no statistically significant OS benefit (10.3 months vs. 7.5 months, $p = 0.093$) [141, 142]. Treatment was well tolerated with mainly GI-side effects (nausea, diarrhea, and abdominal pain) and fatigue. FDA approval was granted recently [143].

Targetable ERBB-2/HER2 overexpression or amplification is observed in 20% of eCCA and 5% of iCCA [144]. Early clinical trials investigating the addition of cetuximab, panitumumab, or erlotinib to cytotoxic chemotherapy or monotherapy with lapatinib were disappointing [145–149]. New ongoing studies focus on the evaluation of antibody-drug conjugates and bispecific antibodies targeting HER2 with promising activity in the early clinical phase [150, 151].

BRAF^{V600E} mutations and TRK fusions are rare events in CCA with a frequency of around 3–5% each [152, 153]. However, phase II basket trials of dabrafenib plus trametinib in BRAF^{V600E} mutated cancers and larotrectinib or entrectinib in TRK-fusion positive cancers showed high RRs (47% for dabrafenib/trametinib, 57% for entrec-

tinib, and 75% for larotrectinib) and durable responses (9 months for dabrafenib/trametinib, 10 months for entrectinib, not reached for larotrectinib) in the biliary tract cancer cohorts [153–155] (Table 1). Entrectinib and larotrectinib are FDA-approved for the treatment of TRK-fusion positive solid tumors.

Immunotherapy

CPI-based immunotherapy has marked a breakthrough in the treatment of a variety of malignancies [156]. CCA is not considered to be a highly immunogenic tumor characterized by a dense desmoplastic and immunosuppressive stroma [157], a low frequency of high microsatellite instability (MSI-H) of around 1–5% [158–160], and a low median tumor mutational burden [161]. Unsurprisingly, results of CPI monotherapy trials have been disappointing so far, except in the small subgroup of MSI-H patients (Table 1). Monotherapy with anti-PD-1 inhibitor pembrolizumab or nivolumab, as well as anti-PD-L1 inhibitor durvalumab was tested in early phase clinical trials in patients with advanced biliary tract cancer and progression upon standard chemotherapy. ORR was low from 3.4% to 13.0%, OS was between 5.2 months and 8.1 months, regardless of PD-L1 expression status [162–164]. However, profound and durable responses upon pembrolizumab monotherapy could be observed in pretreated patients with MSI-H advanced CCA in a phase II trial with an ORR of 40.9% and OS of 24.3 months [165] (Table 1). Two trials investigated the role of double checkpoint inhibition with a combination of PD-1/PD-L1 and CTLA-4 blockade with nivolumab/ipilimumab or durvalumab/tremelimumab to unleash the antitumor immune response in CCA [164, 166]. Activity was slightly increased with an ORR of 11–23% and an OS of 5.7–10.1 months, but at the expense of higher toxicity with 15–23% of patients experiencing relevant adverse events. Several other combination partners with the ability to modify the tumor microenvironment and sensitize CCA to CPI treatment are being investigated. The combination of gemcitabine/cisplatin and durvalumab with or without tremelimumab was investigated in a randomized phase II clinical trial in patients with therapy naïve advanced CCA. Outcomes were favorable with an ORR of 73% and OS between 18.1 and 20.7 months. Two randomized phase III clinical trials are currently assessing the role of combined PD-1/PD-L1 inhibition and gemcitabine/cisplatin in the first-line setting (TOPAZ-1: gemcitabine/cisplatin + durvalumab; NCT03875235, Keynote 966: gemcitabine/cisplatin + pembrolizumab; NCT04003636). Furthermore, the bi-

functional fusion antibody bintrafusp alfa targeting PD-L1 and TGF- β in addition to gemcitabine/cisplatin is being investigated in a phase II/III trial (NCT04066491) in treatment-naïve patients with advanced biliary tract cancer. Other interesting studies with promising results in phase II single-arm studies and the need for investigation in a randomized controlled setting include the combination of pembrolizumab plus multi-kinase inhibitor lenvatinib [167, 168], or pembrolizumab plus granulocyte macrophage colony-stimulating factor [169]. Furthermore, CPI with local therapies such as radiotherapy (NCT03482102), RFA (NCT02821754), or SIRT (NCT04238637) as well as CPI plus PARP inhibitors (NCT03991832) are therapeutic strategies currently assessed in early phase trials. However, new combination regimens could always cause an over-proportionally strong toxicity, as reported by a combination regimen of durvalumab, tremelimumab, and paclitaxel in biliary tract cancer patients [170]. Sponsors and trial physicians should therefore pay special attention to safety signals and adverse events in trials of CPI-based combination regimens.

Conclusion

CCA is a rare and aggressive cancer divided in clinico-pathologically and molecularly distinct subgroups. The treatment of CCA is complex. Interdisciplinary discussion and close cooperation between hepatobiliary and transplant surgery, interventional radiology, endoscopists, and oncologists are mandatory in the treatment of each CCA patient. Given a subset of targetable genetic alterations, molecular profiling for patients with unresectable CCA should be performed as part of the initial diagnostic workup. Advances in targeted therapies, new chemo- and immunotherapy regimens and combinations between systemic treatment and local interventions have the potential to revolutionize the clinical management of the disease and improve patients' outcomes. Treatment of patients in specialized centers with the possibility of inclusion into clinical trials is highly recommended.

Conflict of Interest Statement

N.B.K. has received reimbursement of meeting attendance fees and travel expenses from Eisai and lecture honoraria from Falk. All the other authors have no conflicts of interest to declare.

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