Cancer Treatment and Research Communications 27 (2021) 100354

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

Neoadjuvant therapy for cholangiocarcinoma: A comprehensive literature review

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ARTICLE INFO

Keywords:
Cholangiocarcinoma
Biliary tract cancer
Chemotherapy
Neoadjuvant therapy
Liver cancer
Extrahepatic cholangiocarcinoma

ABSTRACT

Biliary tract cancers (BTCs) comprise a heterogenous group of aggressive and rare malignancies arising in the bile duct outside or within the liver. BTCs include cholangiocarcinoma (CCA), gallbladder cancer (GBC) and ampulla of Vater cancer (AVC); according to the "historical" anatomical classification, CCAs are further subdivided into extrahepatic cholangiocarcinomas (eCCAs) – including distal (dCCA) and perihilar (pCCA) - and intrahepatic cholangiocarcinomas (iCCA). Notably enough, these subtypes reflect distinct features in terms of biology, epidemiology, prognosis and therapeutic strategies. Although surgical resection remains the only potentially curative treatment option for CCA patients, radical surgery is possible for only a small proportion of cases. Moreover, it has been observed that up to 50% of patients deemed resectable at diagnosis are found to be unresectable during exploratory laparotomy. Additionally, even following radical surgery, recurrence rates are high. Neoadjuvant therapy represents an appealing approach in this setting, where this therapeutic strategy has the potential to improve local and distant control, to achieve R0 resection and to prevent distant metastasis. However, few data are currently available supporting neoadjuvant therapy in CCA and several questions remains unanswered, including the activity of systemic therapy in early stages of the disease, the optimal start time of treatment, patient selection and the length of neoadjuvant therapy. In this review, we will discuss available data on neoadjuvant systemic therapy in CCA, highlighting future directions in this setting, with a particular focus on recently published data and ongoing and recruiting trials.

Introduction

The term biliary tract cancer (BTC) encompasses a heterogeneous group of rare malignancies including intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA) - further subdivided into perihilar (pCCA) and distal cholangiocarcinoma (dCCA) - gallbladder cancer (GBC), and ampulla of Vater cancer (AVC) [1, 2]. Of note, this classification reflects important differences not only in terms of anatomical location but also in embryology, epidemiology, molecular features and therapeutic strategies (Fig. 1) [3, 4]. Overall, BTCs constitute the 3% of all gastrointestinal malignancies, representing the second most frequently diagnosed primary liver cancer following hepatocellular carcinoma (HCC) [5, 6]. Although the incidence of CCA reflects geographical differences, with the predominance of these hepatobiliary malignancies in Asia, recent studies have observed that CCA incidence rate is on the rise in most Western countries due to several reasons – including the growing burden of emerging risk factors [7, 8].

CCAs are frequently diagnosed at advanced stage and only a small proportion of patients can be treated with surgical resection [9]. In fact, despite radical surgical resection with negative tumor margins represents the only curative treatment, approximately the 70% of patients are diagnosed with advanced disease – unresectable or metastatic [10, 11]. In these patients, systemic treatment is usually considered the standard of care although loco-regional approaches including radiofrequency ablation and trans-arterial chemo-embolization represent feasible options in selected cases [12, 13]. CCA is largely resistant to systemic chemotherapy and prognosis of patients with advanced disease remains poor [14, 15]. However, several recent reports have identified key oncogenic drivers as possible therapeutic targets in CCA patients, and a wide number of agents have been assessed and are currently under investigation [16-20]. In fact, the molecular landscape of CCA has begun to emerge over the last decade, providing evidence leading to the development of molecularly targeted treatments [21-24].

Adjuvant approaches have been extensively explored in this setting,

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https://doi.org/10.1016/j.ctarc.2021.100354

Available online 16 March 2021

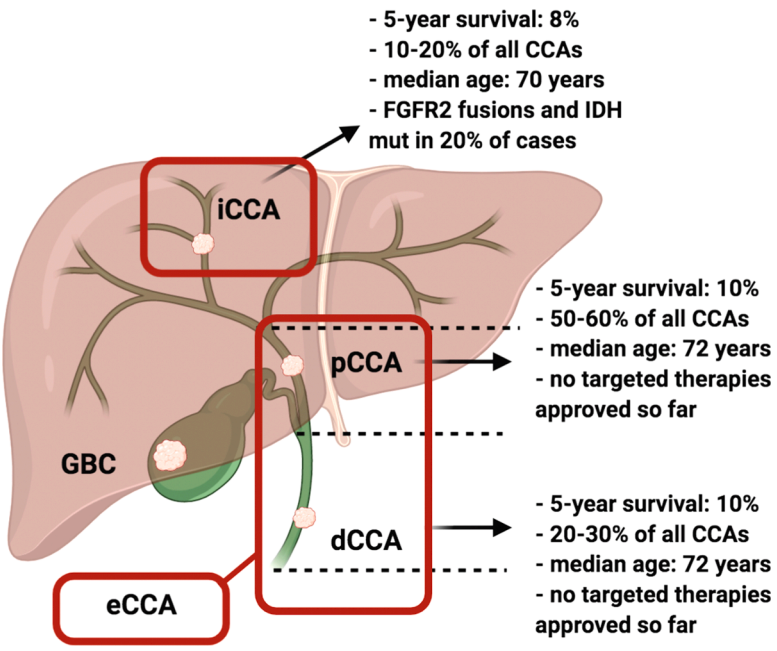

Fig. 1. Schematic representation of the anatomical site and main features of each cholangiocarcinoma subtype. Cholangiocarcinoma includes the intrahepatic, perihilar and distal subtypes; moreover, perihilar and distal cholangiocarcinomas are grouped together in the category of extrahepatic cholangiocarcinoma. *Abbreviations: CCA: cholangiocarcinoma; dCCA: distal cholangiocarcinoma; eCCA: extrahepatic cholangiocarcinoma; FGFR2: fibroblast growth factor receptor 2; GBC: gallbladder cancer; iCCA: intrahepatic cholangiocarcinoma; IDH: isocitrate dehydrogenase; mut: mutations; pCCA: perihilar cholangiocarcinoma.*

with a view to lower the high incidence rate of local and distant relapse in resected CCA patients [25, 26]. Based on the results of a systematic review and meta-analysis by Horgan and colleagues, the use of adjuvant treatment has long been limited on two patient populations [27]: CCAs with nodal involvement and/or those with R1 resection (evidence of microscopic margins positive for tumor). More recently, several trials on adjuvant chemotherapy have been presented and published, reporting controversial results [28, 29]. Among these, the BILCAP study reported longer median OS in patients treated with standard capecitabine compared with those receiving placebo (53 months versus 36 months respectively, Hazard Ratio [HR] 0.75, 95% CI 0.58–0.97; $p = 0.028$) in the pre-specified intention-to-treat sensitivity analysis adjusted for prognostic factors such as nodal status, gender and disease grade [30, 31]. However, the study did not meet its primary endpoint in terms of OS, and capecitabine has not been unanimously accepted as standard of care treatment in completely resected CCA [32].

Although neoadjuvant therapy represents an appealing approach with the aim of acting on micrometastatic disease, of reducing tumor volume, and thus resulting in improved longtime survival, very few data are currently available regarding this therapeutic strategy in CCA [33]. In fact, the majority of data on neoadjuvant treatment for CCAs is limited to retrospective, and often single-institution, case series [34]. However, this strategy has the potential to achieve R0 resection and to provide long-term benefits in this setting. In this review, we provide a comprehensive overview regarding the current landscape of neoadjuvant therapy in CCA, looking at published data and ongoing clinical trials in eCCA and iCCA.

We performed a research on Pubmed/Medline, Cochrane library, and Scopus using the keywords “neoadjuvant treatment” OR “neoadjuvant therapy” OR “neoadjuvant chemotherapy” AND “cholangiocarcinoma” OR “intrahepatic cholangiocarcinoma” OR “extrahepatic cholangiocarcinoma” OR “perihilar cholangiocarcinoma” OR “distal

Table 1
Main studies available in literature assessing neoadjuvant therapy in extrahepatic cholangiocarcinoma. Abbreviations: 5-FU: 5-fluouracil; dCCA: distal cholangiocarcinoma; EBRT: external bearm radiation therapy; mOS: median overall survival; NA: not available; pCR: pathological complete response; PDT: photodynamic therapy; PR: partial response; pts: patients.

Study (year)	Neoadjuvant treatment	Number of patients	Resectable at presentation	R0 / resected, %	Outcomes
McMasters (1997)	5-FU + EBRT	4 dCCAs 5 pCCAs	No	9/9, 100%	No recurrence in pCCA Disease relapse in all dCCA 3 pCR
Gerhards (2000)	EBRT	21 pCCAs	NA	5/21, 23.8%	Disease recurrence in 9 pts (mOS 19 months) No recurrence in 12 pts (mOS 40 months)
Wiedmann (2003)	PDT	7 pCCAs	No	7/7, 100%	Disease recurrence in 2 pts (after 6 and 19 months) No recurrence in 5 pts
Nelson (2009)	5-FU + EBRT ± brachytherapy	12 eCCAs	No	11/12, 91.7%	3 pCR mOS 34 months
Katayose (2015)	Gemcitabine + EBRT	24 eCCAs	Yes	17/21, 80.9%	NA
Kobayashi (2017)	Gemcitabine + EBRT	9 pCCAs	Yes	NA	PR rate 70% 3-year survival 85%
Sumiyoshi (2018)	S-1 + EBRT	8 pCCAs	No	5/6, 83.3%	mOS 31 months 5-year survival 13%

cholangiocarcinoma". Gallbladder cancer was excluded from our paper. We selected the most pertinent and relevant reports considering quality of the studies in terms of statistical analysis, number of patients enrolled, how they were conducted and outcomes. For ongoing clinical trials, we searched in the Clinicaltrials.gov database for recruiting and active, not recruiting trials. We restricted our research to trials focused on the neoadjuvant setting.

Extrahepatic cholangiocarcinoma

Radical surgical resection remains the only potentially curative treatment option for eCCA [35]. As regards dCCA, surgery usually consists of "Whipple procedure", with pancreaticoduodenectomy and reconstruction [36]; conversely, surgery for pCCA is based on extended hepatectomy and bile duct resection inclusive of lymphadenectomy and hepaticojejunostomy [37].

Most of eCCA patients are diagnosed with inoperable disease, defined on the basis of portal vein invasion, biliary infiltration and/or hepatic artery invasion. Several case series with small sample size have been published, reporting the potential effectiveness of combined neoadjuvant therapy in this setting (Table 1). In a retrospective study by McMasters and colleagues, 9 eCCA patients (4 dCCA and 5 pCCA) underwent preoperative chemoradiation prior to surgical resection [38]. Of note, pathologic complete response (pCR) was observed in 3 patients, with the remaining showing different degrees of histologic response [38]; overall, the rate of resection without margins involvement was 100% in the 9 eCCAs. However, although no recurrences were observed in the pCCA group, the 4 dCCAs – despite R0 surgery – relapsed shortly, with a grim prognosis. This report has been probably the first to report that preoperative chemoradiation could play a role as neoadjuvant treatment in eCCA, due to a promising antitumor efficacy.

More recently, several small case series and retrospective studies have been published. Among these, a study by Nelson and colleagues assessing the role of chemotherapy plus radiotherapy in eCCA included 12 patients receiving neoadjuvant treatment consisting of 5-fluorouracil, external beam radiotherapy (EBRT) ± brachytherapy [39]. In this patient population, the rate of R0 resection was 91.7%, with 3 pCR – a result which further supports the possibility of converting patients affected by unresectable eCCA to resectable disease [39]. Similarly, in a study by Jung and colleagues 12 pCCAs received systemic chemotherapy (with 5-fluorouracil or gemcitabine) plus EBRT, reporting a R0 rate of 83.3% and 2 pCR [40]; in addition, downstaging was observed in 11 out of 12 patients (91.7%). Analogous rates of R0 surgery have been highlighted in a phase II study by Katayose and colleagues on 24 eCCA patients receiving neoadjuvant gemcitabine plus EBRT [41]; R0 resection rate was 89.6% among operated cases, with neoadjuvant treatment resulting well tolerated [41]. Another recent Asian experience by Sumiyoshi et al. on 8 pCCAs treated with oral S-1 chemotherapy plus EBRT reported a R0 resection rate of 83.3% [42]. Meta-analysis of aggregate data from these and other recent studies have confirmed that neoadjuvant treatment with chemotherapy plus radiotherapy has the potential to provide important benefits in terms of R0 resection rate [43]. However, randomized controlled trials based on multicenter and large sample size would be recommended to validate these findings.

An alternative treatment strategy exploited by Wiedman and colleagues has been to assess the role of neoadjuvant photodynamic therapy (PDT) in unresectable eCCA [44, 45]. Of note, in a pilot study on 7 pCCAs, neoadjuvant PDT led to R0 resection in all patients. However, despite evidence suggesting that neoadjuvant PDT could be performed safely and could lead to subsequent surgical R0 resection in a selected cohort of patients, few data are available regarding this technique whose role should be explored in properly designed clinical trials [46].

A distinct setting in CCA management is the use of neoadjuvant treatment before liver transplantation (LT) in selected cases of eCCA, with the pivotal protocol proposed by the Mayo Clinic in 1993 [47]. Of note, this protocol has led to the enrollment of CCA patients with unresectable disease according to the following criteria for unresectability: bilateral segment ductal extension, unilateral ductal extension with contralateral vascular encasement, encasement of the main portal vein trunk, and unilateral liver atrophy with contralateral segmental vascular or ductal involvement [48]. Exclusion criteria were history of malignancy within 5 years, prior surgical or percutaneous procedures, prior chemotherapy and/or radiotherapy, and the presence of uncontrolled infections. The included patients were affected by tumors ≤ 3 cm in radial dimension, with no extension below the cystic duct, and no metastases. According to this protocol, chemoradiotherapy consisted of EBRT plus 5-fluorouracil followed by brachytherapy. In the time interval between brachytherapy and transplantation, oral capecitabine was given as maintenance treatment. Subsequently, the protocol criteria were modified, also including patients with CCA extension to the common bile duct [49].

In 2008, Rosen and colleagues reported a large experience on 148 patients with unresectable stage I/II eCCA treated according to the Mayo Clinic Protocol [50]. According to the results shown in this series over 14 years, 1-, 3-, and 5-year patient survival was 82%, 63%, and 55%, respectively. Additionally, 1-, 3-, and 5-year survival following LT was 90%, 80%, and 71%, respectively. Higher recurrence risk was highlighted in elderly patients, with high tumor grade, CA 19–9 $>$ 100 /mL, perineural invasion and/or residual tumor exceeding 2 cm. Although the study raised several criticisms, neoadjuvant chemoradiotherapy followed by orthotopic LT provided interesting clinical outcomes in a highly selected patient population, with durable survival benefits. In addition, similar results were reported in other more recent multicenter studies [51-53]. Further studies are warranted in this setting to detect if chemoradiation plus LT could provide higher benefit compared to curative resection alone – even looking at T1-T2 malignancies – and a French trial (NCT02232932) is currently ongoing, aimed at assessing this question. Of note, chemoradiotherapy in this setting has been associated with a range of adverse events and technical issues, including cholangitis, cholecystitis, and hepatic abscesses, frequently resulting in hospitalization and antibiotics treatment [54]. For example, a report by Mantel and colleagues on eCCA patients receiving the Mayo Clinic treatment observed vascular impairment in the 40% of patients, while arterial and venal complications were reported in the 21% and the 22% of cases, respectively [55].

Intrahepatic cholangiocarcinoma

As in the case of eCCA, surgery remains the only curative therapeutic option and limited data are available on neoadjuvant treatment for iCCA, especially in terms of R0 resection rate [56]. In fact, data are mainly limited to small size cohort studies with different treatment modalities - including radiotherapy, chemotherapy, chemoradiation, and local liver-directed therapies - and heterogeneous approaches, with a R0 resection rate ranging from 30 to 80% [57, 58]. Among these reports, a retrospective single-center study by Kato and colleagues investigated the role of gemcitabine-based chemotherapy as neoadjuvant treatment in 7 iCCA patients with unresectable disease [59]. R0 resection was achieved in 3 patients, with a median OS of 13 months in the included subjects.

In a recent French single-center study, of 74 iCCA patients, the 53% (39/74) underwent surgery following systemic chemotherapy [60]. Of note, the median overall survival of patients with unresectable disease undergoing a median of 6 cycles of chemotherapy plus surgery was 24.1 months. Similarly, the median survival was 25.7 months for resectable patients treated with surgery alone. Thus, similar short- and long-term outcomes were observed in iCCA patients with unresectable disease receiving neoadjuvant chemotherapy plus surgery and in iCCA patients with initially resectable disease.

As regards LT, the use of this technique to treat iCCA remains discussed and controversial, given the high rate of early tumor recurrence and discouraging survival [61]. In fact, few reports assessed

Table 2
Prospective neoadjuvant trials for CCA. Abbreviations: BTC: biliary tract cancer; CCA: cholangiocarcinoma; CT: computed tomography; GemCis: gemcitabine plus cisplatin; iCCA: intrahepatic cholangiocarcinoma; MRI: magnetic resonance imaging; OS: overall survival; pts: patients; TKI: tyrosine kinase inhibitors.

Clinical trial	Pts population	Phase	Neoadjuvant treatment	Compounds description	Estimated enrollment	Primary Outcomes
NCT03603834	CCA	2	mFOLFOXIRI	Oxaliplatin, leucovorin, irinotecan, 5-FU	25	Rate of overall response evaluated by MRI or CT
NCT04308174	BTC	2	Durvalumab + GemCis versus GemCis	Durvalumab: PD-L1 inhibitor	45	R0 resection rate
NCT03579771	iCCA	2	Cisplatin + gemcitabine + nab - paclitaxel		34	Completion of all preoperative and operative therapy Incidence of adverse events
NCT03673072	BTC	3	Cisplatin + gemcitabine		300	OS
NCT04506281	iCCA	2	Gemcitabine + oxaliplatin + lenvatinib + toripalimab	Lenvatinib: TKI Toripalimab: PD-1 inhibitor	128	Event-free survival

neoadjuvant therapy in this setting, despite previous experience with pCCA and dCCA could suggest that neoadjuvant approaches followed by LT could provide long-term benefit in selected patients [62]. In 2018, Lunsford and colleagues reported a case series of 6 iCCA patients receiving neoadjuvant therapy with gemcitabine-based chemotherapy (such as gemcitabine-cisplatin or gemcitabine-capecitabine) followed by LT [63]. In this prospective study, median duration from diagnosis to LT was 26 months and median follow-up from LT was 36 months. Of note, overall survival was 100% at 1 year, 83.3% at 3 years, and 83.3% at 5 years; among the included patients, 3 cases developed disease recurrence at a median of 7.6 months after LT.

Ongoing clinical trials

Chemotherapy

As regards chemotherapy, although the combination of gemcitabine-cisplatin represents the reference doublet for patients with metastatic disease, this treatment is associated with an overall limited response rate (25% according to ABC-02 trial). However, the CCA medical community has tried to explore the role of systemic chemotherapy as neoadjuvant approach.

As previously reported, the vast majority of studies on the topic of neoadjuvant treatment in CCA is limited to retrospective, small sample size case series [64, 65]. However, some prospective studies are assessing the role of neoadjuvant treatment in BTC, trying to translate previous experience of pancreatic cancer in this setting (Table 2). Among these, a phase II trial (NCT03603834) is evaluating the efficacy of modified FOLFOXIRI (combination of fluorouracil, folinic acid, irinotecan, and oxaliplatin) for borderline resectable CCA. The primary outcome of this trial is the rate of overall response evaluated by magnetic resonance imaging or computed tomography according to RECIST 1.1 criteria. The study has a planned enrollment of 25 subjects with an estimated primary completion date in August 2023.

A phase II, single-arm trial (NCT03579771) is currently assessing the combination of gemcitabine plus cisplatin plus Nab-paclitaxel as neoadjuvant chemotherapy in patients with stage IB, stage II, stage IIIA, and stage IIIB iCCA. The primary outcomes measures include the following: completion of all preoperative and operative therapy; incidence of adverse events). The study has a planned enrollment of 34 subjects with an estimated primary completion date in September 2021.

Immunotherapy

The phase II DEBATE trial (NCT04308174) is randomizing patients with resectable CCA to durvalumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone as preoperative treatment. The primary endpoint of this study is R0 resection rate, with overall survival, event-free survival, adverse events, response rate also assessed as secondary endpoints. The DEBATE trial has an estimated completion date in September 2021, with a planned enrollment of 45 patients.

Similarly, an ongoing phase II study (NCT04506281) is evaluating the role of the combination of the PD-1 antibody toripalimab combined with GEMOX chemotherapy as neoadjuvant approach for resectable iCCA with high-risk recurrence factors. Event-free survival represents the primary outcome of this trials, with has overall survival, objective response rate, pathological remission rate, and adverse events as secondary endpoints.

Targeted therapies

Targeted therapies have the potential to represent a future direction of neoadjuvant therapy in CCA. In fact, next-generation sequencing (NGS) has led to deeper molecular profiling of BTC, opening the era of targeted agents in this setting. However, no clinical trials are currently exploring the role of these agents as neoadjuvant approach, something that warrants further investigation on novel therapies.

TACE

Transarterial chemoembolization (TACE) has been explored as neoadjuvant approach in CCA patients [66]. In particular, a study conducted by Herber and colleagues on 15 iCCA patients receiving TACE (performed with a mixture of 10 ml Lipiodol and 10 mg mitomycin C injected into the tumor-supplying vessels), observed stable disease in 60% of patients, with partial response in 7%. In addition, complete response was reported in 7% of subjects, with median OS of included patients of 21.1 months [67]. Subsequently, a study by Vogl reported stable disease in 57% of 115 iCCA patients receiving TACE, with median OS of 13 months [68]. Despite these promising results, the findings by Herber and Vogl have not been confirmed by more recent trials.

Conclusions

Although neoadjuvant systemic treatment is supposed to increase R0 resection rate, few data are currently available regarding the role of this therapeutic approach in CCA, and there is no general consensus on neoadjuvant therapy in this setting. However, combined approaches have provided interesting results, with these treatments having the potential to provide survival benefits in selected group of patients. Further data from well-designed, prospective clinical trials are warranted.

Competing interest statement

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.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declaration of Competing Interest

No conflict of interest to declare by all authors.

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