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Review Article

Intrahepatic cholangiocarcinoma: Evolving role of neoadjuvant and targeted therapy

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Intrahepatic cholangiocarcinoma is an aggressive, often fatal, malignancy that arises from the bile ducts. As it often presents with metastatic disease, surgery has limited utility. However, in some cases, neoadjuvant chemotherapy has provided the necessary reduction in tumor burden to allow for adequate resection. Consequently, new advances in neoadjuvant chemoradiation and targeted therapy are of interest with numerous case reports and small series published routinely; it is challenging to present a large case series or study given the overall rare frequency with which this malignancy is seen. Herein, we aim to summarize the newest advances in both neoadjuvant chemotherapy and targeted immunotherapy.

Key Words: Cholangiocarcinoma; Neoadjuvant treatment; Targeted; Immunotherapy

INTRODUCTION

Cholangiocarcinoma (CCA) is an aggressive malignancy that arises from the bile duct cholangiocytes and it is classified into intrahepatic CCA (iCCA) and extrahepatic CCA (eCCA). iCCA arises from the peripheral bile ducts within the liver parenchyma, proximal to the secondary biliary radicals. iCCA represents approximately 10% to 20% of all cholangiocarcinoma cases and has a 5-year survival rate of 8% [1].

MAIN TEXT

In the early stages of iCCA, surgery has historically been thought to be the only chance for cure. However, given its oftentimes late detection and metastatic presentation, over 65% of iCCA patients present with unresectable disease or a disease stage that is not suitable for resection [2]. Consequently, the prognosis for iCCA is very poor and disease free and overall survival in patients who have undergone surgery are still dismal with a reported 5-year overall survival rate of 10% to 35% [3-5]. Historic outcomes of liver transplant in patients with iCCA are discouraging too with a reported 5-year survival rate < 25% [6,7]. The high incidence of early recurrence, even among patients with localized disease who undergo margin-negative resection, have resulted in a sustained interest towards advancement in adjuvant systemic therapy. The recently concluded Japanese JCOG1202 Trial further asserts the effectiveness of adjuvant capecitabine following resection of any biliary tract carcinoma (BTC), including iCCA [8]. The use of adjuvant gemcitabine and cisplatin following R0 or R1 resection of any BTC including iCCA is currently being investigated (ACTICCA-1 trial) [7].

The role of preoperative transarterial chemoembolization (TACE) and transarterial radioembolization with yttrium-90 (TARE) have also been investigated in patients with iCCA. A large retrospective study that used TACE on 127 patients with advanced iCCA reported partial response in 19 (15.0%) patients, stable disease in 101 (79.5%), and progressive disease (PD) in 7 patients (5.5%), 3 months after therapy, with no complete responses. Only 4% of the patients were downsized and successfully underwent resection. Studies on TARE have reported similar low conversion rates (between 4% and 11%) [9-11]. However, concomitant use of TACE/TARE with systemic

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therapy has shown promising results in recent studies [12,13].

Though neoadjuvant chemotherapy has proven efficacy in other resectable cancers, its indication in iCCA is limited to locally advanced/unresectable tumors. It is no surprise that most literature describing the use of neoadjuvant therapy (NT) in iCCA has stemmed from retrospective studies that have included patients with locally advanced and unresectable tumors receiving NT. Studies that have looked at gemcitabine-based NT have reported the conversion of locally advanced/unresectable tumors to resectable in approximately 22% to 53% of patients [14-16]. A systematic review that included 18 studies with 1,880 patients reported significantly longer survival in patients who underwent resection following downstaging with NT than those who did not (29 vs. 12 months) [17]. There is a growing body of literature examining the role of liver transplantation in iCCA following NT. Lunsford et al. [18] reported on 6 patients with iCCA who received either gemcitabine-cisplatin or gemcitabine-capecitabine-based therapy and subsequent liver transplantation. There was a relatively high recurrence with 3 of the liver transplantation patients developing recurrence, but overall survival was higher than usual with 100% (all 6 patients) surviving to 1 year and 83.3% (5 out of 6 patients) alive at 5 years [18]. The ongoing trials investigating the role of NT in resectable candidates will pave the way for a standard of care in iCCA in the future (Table 1).

Despite being the backbone of the current systemic therapy, platinum-based chemotherapy is often limited by its narrow therapeutic index and harsh cytotoxic side effects. Targeted molecular therapy is a growing area of interest in nearly all oncological fields, and cholangiocarcinoma is no exception. Next-generation sequencing has aided the identification of specific genetic mutations driving cholangiogenesis. Inhibiting critical molecular pathways or mutant proteins with targeted therapy can arrest tumor progression and facilitate tumor regression. A better understanding of intratumor heterogeneity has further paved the way for immunotherapeutic strategies in the management of iCCA. Adoptive cell therapy and immune checkpoint inhibitors (ICI) ascertain the role of immunotherapy to enhance natural, anti-tumor immune responses enabling the generation of anti-tumor memory and long-lived tumor destruction.

ICI targeting programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen-4 (CTLA-4) seem to play a pivotal role in countering the tumor-tolerant microenvironment in iCCA [19]. Immunotherapies targeting PD-1 and its associated ligand are increasingly gaining interest. Lack of mismatch repair proteins or microsatellite instability occurs in approximately 10% of iCCA patients and hence these patients are good targets for immunotherapy [20]. Based on encouraging results from PD-L1 blockade, the United States Food and Drug Administration (FDA) approved pembrolizumab for microsatellite instability high/mismatch repair deficient tumors in 2017 [20]. In a retrospective review of patients with advanced biliary tract cancers, in a propensity score matching analysis, Gou et al. [21] found that anti-PD-1 therapy, in addition to chemotherapy, resulted in prolonged progression-free survival compared to patients who received chemotherapy alone. A case report by Zhang et al. [22] demonstrated that neoadjuvant PD-1 blockade and tyrosine kinase inhibitor therapy in a 38-year-old female with iCCA resulted in an R0 resection with prolonged survival. The DEBATE Trial (Neoadjuvant Gemcitabine Plus Cisplatin With or Without Durvalumab in Resectable Biliary Tract Cancer) is currently recruiting patients and the trial results will hopefully guide

Table 1. Active and Pending National Clinical Trials.gov Registered Trials for neoadjuvant chemotherapy for intrahepatic cholangiocarcinoma

Trial ID	Author/institution	No. of patients	Arm(s)	Primary outcome	Status
NCT04961788	Shanghai Zhongshan Hospital	30	Toripalimab + Gemox	12-month ORR	Recruiting
NCT04989218	University of Alabama at Birmingham	20	Durvalumab, Tremelimumab + platinum-based chemotherapy	12-week (4 cycle) ORR	Recruiting
NCT04523402	Shen Feng, Eastern Hepatobiliary Surgery Hospital	100	Oxaliplatin + Gemcitabine & Resection versus Resection only	24-month PFS	Not yet recruiting
NCT05290116	Sun Yat-sen University	17	Hepatic Arterial Infusion Chemotherapy + Tislelizumab and Apatinib	12-month ORR	Recruiting
NCT04954781	Fudan University	25	Transarterial chemoembolization + Tislelizumab	24-month ORR	Recruiting
NCT04546828	Samsung Medical Center	34	Gemcitabine, Cisplatin, Nab-Paclitaxel	16-week increased rate of R0 resection	Withdrawn
NCT04669496	Shanghai Zhongshan Hospital	178	Gemox + Lenvatinib, Toripalimab versus Capecitabine	24-month EFS	Recruiting
NCT04523402	Eastern Hepatobiliary Surgery Hospital	100	Gemox vs No neoadjuvant	24-month EFS	Not yet recruiting

ORR, overall response rate; PFS, progression-free survival; EFS, event-free survival.

Table 2. Active and Pending National Clinical Trials.gov Registered Trials for immunotherapy for intrahepatic hepatic cholangiocarcinoma

Trial ID	Author/institution	No. of patients	Arm(s)	Target of drug	Phase	Setting	Primary outcomes measured	Status	Preliminary outcomes[a)]
NCT02829918	H. Lee Moffitt Cancer Center	54	Nivolumab	PD-1	II	Unresectable	16-month ORR, 36-month OS, PFS	Active, not recruiting	ORR after 4 cycles of treatment is 22%, average PFS is 3.68 months (2.30–5.69 months)
NCT03046862	Seoul National University Hospital	31	Durvalumab + Tremelimumab + Gemcitabine/Cisplatin	PD-L1, CTLA-4	II	Unresectable or recurrent cancer	RR at 6 weeks, PFS, OS	Active, not recruiting	N/A
NCT05223816	Virogin Biotech Ltd.	41	VG161	PD-L1	IIa/IIb	Unresectable	3-month PFS & 12-month ORR	Active, not recruiting	N/A
NCT04361331	Shanghai Zhongshan Hospital	60	Lenvatinib + Toripalimab versus Lenvatinib + Gemox chemotherapy	PD-1	II	Unresectable	12-month ORR	Active, not recruiting	N/A
NCT03260712	European Organisation for Research and Treatment of Cancer	50	Gemcitabine + Cisplatin + Pembrolizumab	PD-1	II	Unresectable	6-month PFS	Active, not recruiting	N/A
NCT03473574	AIO-Studien-gGmbH	128	Durvalumab + Tremelimumab + Gemcitabine +/– Cisplatin	PD-1, CTLA-4	II	Unresectable	30-month ORR	Active, not recruiting	N/A
NCT03875235	AstraZeneca	810	Gemcitabine + Cisplatin +/– Durvalumab	PD-1	III	Unresectable	40-month OS	Active, not recruiting	Combining Durvalumab: OS 12.8 months (11.1–14.0 months), OS at 18 months 35.1%, PFS 7.2 months (6.4–7.4 months) Without Durvalumab: OS 11.5 months (10.1–12.5 months), OS at 18 months 25.6%, PFS 5.7 months (5.6–6.7 months)
NCT03201458	National Cancer Institute	76	Atezolizumab +/– Cobimetinib	PD-L1, MEK	II	Unresectable	12-month PFS	Active, not recruiting	N/A
NCT03101566	University of Michigan Rogel Cancer Center	64	Nivolumab + Gemcitabine/Cisplatin	PD-1, CTLA-1	II	Unresectable	6-month PFS	Active, not recruiting	% of patients alive and without disease progression at 6 months Gemcitabine + Cisplatin + Nivolumab 59.4% vs. Nivolumab + Ipilimumab 21.2%

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Table 2. Continued 1

Trial ID	Author/institution	No. of Patients	Arm(s)	Target of drug	Phase	Setting	Primary outcomes measured	Status	Preliminary outcomes[a)]
NCT03785873	University of Michigan Rogel Cancer Center	34	Nivolumab + Nanoliposomal-Irinotecan, 5-FU, Leucovorin	PD-1	Ib/II	Unresectable	4-week AE rate, 2-year PFS	Active, not recruiting	N/A
NCT02821754	National Cancer Institute	54	Durvalumab + Tremelimumab +/– TACE + RFA or Cryoablation	PD-1, CTLA-4	II	Unresectable	6-month PFS, AE rate	Active, not recruiting	6 month PFS, 36 patients in RFA/TACE group; average month survival is 2.8 months (1.3–4.8 months), only 1 patient in RFA/cryoablation group and still alive
NCT03046862	Seoul National University Hospital	31	Durvalumab + Tremelimumab + Gemcitabine/Cisplatin	PD-1, CTLA-4	II	Unresectable	6-week RR	Active, not recruiting	N/A
NCT03230318	Basilea Pharmaceutica	148	Derazantinib	FGFR2	II	Unresectable	32-week ORR & PFS	Completed	N/A
NCT03639935	University of Michigan Rogel Cancer Center	35	Rucaparib + Nivolumab	PD-1, PARP	II	Unresectable	4-month OS, PFS	Recruiting	N/A
NCT03867370	Shangai Junshi Bioscience	40	Toripalimab + Lenvatinib	PD-1	Ib/II	Neoadjuvant Treatment	Pathological Response Rate, 2-month ORR, R0 resection rate	Recruiting	N/A
NCT03704480	GERCOR – Multidisciplinary Oncology Group	106	Durvalumab + Tremelimumab +/– Paclitaxel	PD-1, CTLA-4	II	Unresectable	6-month OS	Recruiting	N/A
NCT03898895	Sun Yat-sen University	36	Camrelizumab + Radiotherapy	PD-1	II	Unresectable	12-month PFS, OS, AE rate	Recruiting	N/A
NCT05251662	Tianjin Medical University Cancer Institute and Hospital	90	GEMOX + Bevacizumab + Sintilimab vs Sintilimab + GEMOX	PD-L1	II	Unresectable	90-day ORR	Recruiting	N/A
NCT03482102	Massachusetts General Hospital	70	Tremelimumab + Duravalumab + Radiation	PD-1, CTLA-4	II	Unresectable	3-year ORR, AE rate	Recruiting	N/A
NCT03695952	Asan Medical Center	100	Nivolumab or Pembrolizumab	PD-1	Pros-pective Cohort	Unresectable	6-month ORR, AE rate	Recruiting	N/A
NCT03796429	Shanghai Zhongshan Hospital	40	Gemcitabine + Cisplatin + Toripalimab (up to 2 years)	PD-1	II	Unresectable	36-month PFS	Recruiting	N/A

Table 2. Continued 2

Trial ID	Author/institution	No. of Patients	Arm(s)	Target of drug	Phase	Setting	Primary outcomes measured	Status	Preliminary outcomes[a)]
NCT03478488	3D Medicines Co.	480	KN035 +/– Gemcitabine/ Oxaliplatin	PD-L1	III	Unresectable	12-week OS	Recruiting	N/A
NCT04295317	Shanghai Zhongshan Hospital	65	Capecitabine + SHR-1210	PD-1	II	Unresectable	24-month Recurrence free survival	Recruiting	N/A
NCT04301778	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	30	Durvalumab + SNDX-6352	PD-1, CSF-1R	II	Unresectable	4-year ORR and drug-AE	Active, not recruiting	N/A
NCT05052099	University Hospital, Essen	35	FOLFOX6 + Atezolizumab + Bevacizumab	PD-1, VEGF	1b/II	Unresectable	12-week ORR	Recruiting	N/A
NCT01853618	National Cancer Institute	61	Tremelimumab +/– RFA +/– TACE	CTLA-4	I	Unresectable	12-month AEs, PFS, OS	Completed	PFS 8.6 months for Tremelimumab + Cryoablation as compared to 3.4 months for Tremelimumab + RFA
NCT03110328	Samsung Medical Center	33	Pembrolizumab	PD-1	II	Unresectable, second-line treatment	12-month ORR, PFS, OS	Completed	N/A
NCT03111732	National Cancer Institute	11	Pembrolizumab + Oxaliplatin/ Capecitabine	PD-1	II	Unresectable	5-month PFS	Completed	Median amount of time patient survives without disease progression for 5 months after treatment, Pembrolizumab + Oxaliplatin + Capectitabine, 4.54 months (2.5–9.6 months)

RR, response rate; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; AE, adverse events; RFA, radiofrequency ablation; TACE, Transarterial Catheter Chemoembolization; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor; PARP, poly (ADP-ribose) polymerase; FGFR, fibroblast growth factor receptor.

[a)]Preliminary Selected Outcomes as of 12/20/2022. Not all preliminary data reported had an accompanying statistical analysis.

future PD-L1 treatment of cholangiocarcinoma [23]. Another study examining the role of anti-PD-L1, titled "PD1 Antibody (Toripalimab), GEMOX, and Lenvatinib Neoadjuvant Treatment for Resectable Intrahepatic Cholangiocarcinoma with High-Risk Recurrence Factors" is also recruiting patients. There is early, emerging, data from Moffitt Cancer Center, AstraZeneca, and Michigan Cancer Center trials demonstrating that PD-1 antibodies, Nivolumab and Durvalumab, have improved progression-free survival and overall survival (NCT02829918, NCT03875235, NCT03101566). This data, while just preliminary, has shown that PD-1 therapy is more effective in monotherapy than when combined with gemcitabine-cisplatin. There is also data from the National Cancer Institute study examining the combination of PD-1 antibody (Durvalumab) with CTLA-4 antibody (Tremelimumab) and TACE/RFA versus Cryoablation, but at this time that study has too few patients (cryoablation arm only has 1 patient currently reported in it) to draw conclusions from.

Isocitrate dehydrogenase (IDH) mutations are found in approximately 13% to 14% of iCCA patients [24,25]. In a multi-center, randomized, double-blinded study involving 124 patients with chemotherapy-refractory disease, Ivosidenib (IDH-1 inhibitor) provided overall improved progression-free survival compared to those receiving the placebo [26]. IDH2 inhibitors such as Enasidenib are currently being tested in clinical trials.

The rate of fibroblast growth factor receptor (FGFR) 2 mutations in iCCA is approximately 13% to 15% [27]. Abou-Alfa et al. [28] in 2020, described the use of Pemigatinib (a selective, oral FGFR1-3 inhibitor and the first FDA-approved targeted agent for the second-line treatment of iCCA) in 107 patients with confirmed FGFR2 mutations. Complete response was reported in 3 patients (2.8%), a partial response in 35 (32.7%), and stable disease in 50 (46.7%) [28]. Overall survival was 21.1 months and progress-free survival was approximately 6.9 months [28]. A Phase II trial examining the role of BGJ398 (FGFR kinase inhibitor) demonstrated an overall response rate of 14.8%, progression-free survival of 5.8 months, and disease control rate of 75.4% [29].

While BRAF and MEK mutations are believed to be relatively rare mutations in biliary tract malignancies, a combination of BRAF inhibition (using Dabrafenib) and MEK inhibition (using Trametinib/Selumetinib) seems to have a synergistic impact with improved results in several phase II trials including the ROAR Basket Trial [30-33]. Mutations in Human Epidermal Growth Factor Receptors have been noted in 8% of iCCA patients [34,35]. The combination of erlotinib (EGFR tyrosine kinase inhibitor) and bevacizumab (vascular endothelial growth factor inhibitor) studied in a phase II trial on 49 patients with advanced BTC described partial response in 6 patients (12.2%) and stable disease in 25 patients (51.0%) [34]. Early investigations into inhibiting EGFR with Pantumumab for unresectable tumors have not shown significant improvement in disease free survival [36]. Mutations in BRCA1 and BRCA2 carry an increased risk of developing cholangiocarcinoma given DNA repair pathway mutations [34]. In a retrospective cohort study by Golan et al. [37], which included 7 patients with iCCA, treatment with poly-ADP ribose polymerase inhibitors resulted in a favorable response, with one patient's overall survival censored at 64.76 months and progression-free survival of 42.6 months.

There is also an increased emphasis by the scientific community on examining Wnt/[Symbol - b]-catenin signaling, Hedgehog signaling, and JAK/STAT pathways which are all involved in cell growth, cell death, and proliferation [38]. The increased activation in these pathways is thought to be secondary to increased IL-6 secretion by activated Kupffer cells, and other cells activated by cancer pathogenesis, including tumor-associated macrophages and fibroblasts [38]. Increased IL-6 can also result in STAT3 overexpression and loss of negative feedback of JAKs [39]. Early cellular studies investigating these pathways are underway, with the hope of inhibiting the Wnt pathway in the progression to uncontrolled metastatic growth of cholangiocarcinoma cells [40].

CONCLUSIONS

Though the use of immune/targeted therapy in iCCA is at present under investigation, the surfeit of ongoing clinical trials is exciting; the results of which are eagerly anticipated. While most of these targeted therapies are currently being investigated in patients with advanced disease and early phase trials, these therapies hold great potential for use in the neoadjuvant and perioperative settings. Limited success with immune checkpoint blockade mono therapy has led to more trials that are studying combination strategies for enhanced efficacy, which include dual immune checkpoint blockade (ICB) or constituting of ICB along with chemotherapy and/or targeted therapy (Table 2). Acknowledging the tumor microenvironment and genetic heterogeneity displayed by iCCA is essential to furthering the therapeutic potential of ICI and targeted therapy. The next frontier in the treatment of iCCA awaits the development of predictive biomarkers that can both guide iCCA treatment decisions and predict response to immune/targeted therapy. A better understanding of the synergy associated with combinational therapeutic approaches and the advent of precise biomarkers may well represent the future direction of NT in iCCA.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

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