Review

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Treatment of biliary tract carcinoma over the last 30 years

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SUMMARY Surgical resection could offer the only chance of a long-term cure for biliary tract carcinoma. However, only a small percentage of these patients can undergo surgery based on the progression of the disease. Most patients with biliary tract carcinoma receive palliative chemotherapy. Until 2010, patients with unresectable biliary tract carcinoma received fluorouracil (5-FU), gemcitabine (GEM), and cisplatin (CDDP)-based chemotherapies. The ABC-02 study established GEM with CDDP as the first-line therapy for patients with unresectable biliary tract carcinoma, and phase III studies indicated that several combinations of anti-cancer drugs such as GEM with S-1 benefited patients. In contrast, clinical studies on targeted therapy dosages for biliary tract carcinoma in the 2010s failed to corroborate the advantages of administering cancer treatment with or without other anticancer drugs. Due to the easy access to cancer panels, precision medicines (such as ivosidenib for *IDH1* mutations, pemigatinib for *FGFR2* fusions, and entrectinib and larotrectinib for *NTRK* fusions) were recently found to be effective in the treatment of patients with these genetic alterations. Moreover, many clinical studies on immune checkpoint inhibitors for advanced biliary tract carcinoma are currently underway and could provide more effective treatment options in the near future.

Keywords biliary tract carcinoma, chemotherapy, anti-cancer drug, targeted therapy, precision medicine, immune checkpoint inhibitor

1. Introduction

Biliary tract carcinoma refers to a group of malignancies of the biliary epithelium. Based on anatomical origin, biliary tract carcinoma is classified into the following categories: intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, distal cholangiocarcinoma, gallbladder carcinoma, and ampullary cancer (*1*). Pathologically, most of these tumors are adenocarcinoma (*2*). Surgical resection with negative margins and porta hepatis lymphadenectomy is the standard of care and offers the only chance of a long-term cure (*3*).

However, only a few patients with biliary tract carcinoma are eligible for curative surgery because of metastasis to distant sites and lymph nodes and direct invasion of the major vessels (*4*). Moreover, even patients who undergo curative resection have poor outcomes due to the high rate of tumor recurrence (*1*). Therefore, the development of non-surgical treatment options is a pressing issue for patients with biliary tract carcinoma.

Chemotherapy is performed using a drug or a combination of drugs and is a palliative treatment option for patients with advanced disease. Anti-cancer drugs such as fluorouracil (5-FU), gemcitabine (GEM), and cisplatin (CDDP) are cytotoxic; they kill tumor cells by inhibiting the division of rapidly growing cells, yet they simultaneously affect normal cells that have fast proliferation rates. However, targeted therapies are cytostatic and use monoclonal antibodies or small molecule inhibitors that act on specific molecular targets that are associated with cancer to induce the death of tumor cells via apoptosis and stimulation of the immune system. When used in combination with anticancer drugs, targeted therapies deliver anticancer drugs to cancer cells, consequently minimizing undesirable adverse reactions (*5,6*).

The current review has focused on the 30-year history of chemotherapy for advanced biliary tract carcinoma, including anticancer drugs, targeted therapies, precision medicine, and immunotherapies. Here, a systemic review of the literature was conducted to estimate the level of evidence supporting the use of a chemotherapy regimen for patients with advanced biliary tract carcinoma.

2. First-line chemotherapy

Patients with advanced biliary tract carcinoma receive

Table 1. Chemotherapy for biliary tract carcinoma (phase III and randomized comparative phase II trials) (> 80 patients)

Author	Trial	Patient No.	Year	Regimen	Primary end point	Remarks	*Ref.*
First-line chemotherapy							
Glimelius		90	1996	5-FU with/without etoposide *vs*. BSC	NA	including pancreatic cancer	(*10*)
Valle	ABC-02	410	2010	GEM/CDDP *vs*. GEM	OS		(*7*)
Okusaka		84	2010	GEM/CDDP *vs*. GEM	1-year OS		(*24*)
Sharma		82	2010	GEMOX *vs*. BSC *vs*. FUFA	OS	Gallbladder carcinoma	(*28*)
Kim		224	2019	XELOX *vs*. GEMOX	6-mo PFS	Not inferior	(*30*)
Morizane	JCOG1113	354	2019	GEM/CDDP *vs*. GEM/S-1	OS	Not inferior	(*31*)
Second-line chemotherapy							
Lamarca	ABC-06	162	2021	FOLFOX *vs*. BSC	OS		(*36*)
Adjuvant chemotherapy							
Primrose	BILCAP	447	2019	Capecitabine *vs*. Observation	OS		(*41*)

GEM, gemcitabine; CDDP, cisplatin; OS, overall survival; BSC; best supportive care; FUFA, 5-FU plus folinic acid; XELOX, capecitabine plus oxaliplatin; GEMOX, gemcitabine plus oxaliplatin; FOLFOX, 5-FU plus oxaliplatin; PFS, progression-free survival.

chemotherapy as the main treatment when surgical resection is not an option. However, randomized control trials involving large cohorts were not conducted until 2010, when the ABC-02 study proved that combination chemotherapy using GEM and CDDP was associated with longer patient survival (*7*). It remains one of the options for first-line treatment of unresectable biliary tract carcinoma (Table 1).

2.1. Fluorouracil-based chemotherapy

In the late 1980s and 1990s, 5-FU-based chemotherapy yielded modest results in patients with unresectable biliary tract carcinoma (*8-11*). In a prospective randomized Eastern Cooperative Oncology Group (ECOG) study, 53 patients with advanced gallbladder cancer and 34 with advanced bile duct cancer were treated with oral 5-FU-based chemotherapy (oral 5-FU alone or oral 5-FU with streptozotocin or oral 5-FU with methyl-CCNU), and about 10% of patients had an objective response (*9*). In the late 1990s, a small-scale randomized study indicated that chemotherapy (5-FU with/without etoposide) was effective for patients with unresectable biliary tract or pancreatic cancer compared to best supportive care (median overall survival [OS] time, 6.0 months *vs*. 2.5 months) (*10*). The overall response rate to 5-FU modulated with leucovorin was 32%, indicating that the regimen could lead to prolonged patient survival (*8*). A phase II trial indicated that a regimen of 5-FU, doxorubicin, and mitomycin C was also effective, and a partial response was achieved in 31% of patients with advanced or recurrent biliary tract carcinoma (*12*). Besides 5-FU, single agents, such as CDDP and mitomycin C, do not have significant antitumor activity against biliary tract carcinoma (*13,14*).

2.2. Gemcitabine alone

GEM is a nucleotide analog with biological activity against a broad spectrum of solid tumors such as pancreatic, breast, and lung cancers (*15*). It has remarkable efficacy against advanced biliary tract carcinoma and is now considered to be a key drug to treat these neoplasms (*16*). Several phase II studies with GEM alone (a dosing regimen of 1,000-2,200 mg/m^2, GEM administered over 30 min weekly for two or three weeks with a week of rest) were reported in the early 2000s (*17-20*). These trials had a response rate ranging from 12 to 36% within an acceptable level of toxicities and median OS of 7.2 to 11.5 months.

2.3. Gemcitabine in combination with platinum compounds

Later, phase II trials using GEM in combination with other agents were reported. In the early 2000s, the median OS of patients with advanced biliary tract carcinoma receiving GEM with a 5-FU infusion along with intravenous infusion of leucovorin ranged from 4.7 to 9.7 months (*21,22*). In the late 2000s, many phase II studies that included > 30 patients by arm assessed a combined regimen of GEM and CDDP (GEM/CDDP) (*23*). The administered dosage was 1,000 or 1,250 mg/m^2 and 20−80 mg/m^2, respectively. In a meta-analysis of 16 studies using the GEM and CDDP combination, the median OS was 9.8 months (range: 5.0−15.2 months).

In 2010, the multicentric phase III ABC-02 study established GEM (1,000 mg mg/m^2) with CDDP (25 mg mg/m^2) as the standard of first-line therapy for patients with unresectable biliary tract carcinoma, and it continues to be standard first-line chemotherapy (*7*). GEM with CDDP resulted in a significant survival advantage as chemotherapy for advanced biliary tract carcinoma; patients who were treated with GEM/CDDP lived longer than those treated with GEM alone in terms of OS (median: 11.7 *vs*. 8.1 months, $P < 0.001$) and progression-free survival (PFS) (8.0 *vs*. 5.0 months, $P < 0.001$). The effectiveness of this regimen was reproducibly demonstrated in a randomized phase

II study in Japan (median OS: 11.2 months *vs*. 7.7 months) (*24*).

In the late 2010s, GEM plus nab-paclitaxel became a standard treatment regimen for advanced biliary tract carcinoma (*25,26*). The median OS and PFS of 74 patients who received intravenous nab-P and GEM were 12.4 and 7.7 months, respectively (*26*). Moreover, a better PFS (median, 11.8 months) and OS (19.2 months) were indicated in a phase II study using nab-paclitaxel in addition to GEM/CDDP for 62 patients with advanced biliary tract carcinoma (*27*).

Oxaliplatin is a third-generation platinum compound that causes much less nausea, vomiting, and renal toxicity, but it has a high rate of peripheral neuropathy compared to high-dose CDDP. Besides the GEM/CDDP regimen, phase II studies using GEM with oxaliplatin (GEMOX) for advanced biliary tract carcinoma were reported in the late 2000s (*23*). A meta-analysis of data of the 14 GEMOX group indicated that median OS was 10 months (range: 8.8−11 months), suggesting that GEMOX could be considered as a standard equivalent to GEM/CDDP. A study by Sharma *et al*. was the only phase III study to find that GEMOX helped to prolong OS in patients with advanced gallbladder carcinoma compared to those receiving best supportive care (median OS: 9.5 *vs*. 4.5 months, $P = 0.039$) in 2010 (*28*).

Capecitabine is an oral fluoropyrimidine prodrug that exhibits preferential conversion to 5-FU in tumor tissue. Capecitabine plus oxaliplatin (XELOX) has also displayed modest activity against biliary tract carcinoma (*29,30*). In a 2019 phase III study, the median OS was 10.4 months for the GEMOX group and 10.6 months for the XELOX group ($P = 0.131$), and the median PFS was 5.3 months and 5.8 months ($P = 0.171$), respectively (*30*). Grade 3 to 4 adverse events did not differ significantly between the two groups. However, the XELOX group had a significantly lower frequency of hospital visits due to the oral administration of capecitabine. The aforementioned randomized trial indicated that XELOX was not significantly inferior to GEMOX in terms of the 6-month PFS rate.

2.4. GEM in combination with S-1

S-1 is an oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine based on biochemical modulation of 5-FU, and it results in a high 5-FU concentration in the blood for a long duration. In 2019, the JCOG1113 study indicated that GEM plus S-1 (GEM/S-1) was not inferior in treating advanced biliary tract carcinoma, and it had an acceptable toxicity profile compared to GEM/CDDP in a phase III study (median OS, 15.1 months *vs*. 13.4 months; median PFS, 6.8 months *vs*. 5.8 months) (*31*). That study was the first to provide positive results for advanced biliary tract carcinoma since the ABC-02 study. Unlike GEM/CDDP, the GEM/S-1 regimen does not require hydration; therefore, it became a convenient standard option for patients with advanced biliary tract carcinoma. Moreover, the TG 1308 study, a phase II trial using a modified GEM/S-1 regimen, noted a moderate efficacy (median OS, 12.7 months, and median PFS, 5.4 months) with a favorable safety profile in patients with advanced biliary tract carcinoma in 2020 (*32*).

3. Second-line chemotherapy

Available evidence from the phase III ABC-02 and JCOG1113 studies indicated that GEM/CDDP and GEM/S-1 are the standard first-line chemotherapy regimens for advanced biliary tract carcinoma (*7,31*). After standard first-line chemotherapies, however, there is little available evidence to propose second-line chemotherapy for the disease.

In the mid-2010s, multicentric retrospective studies using various types of regimens indicated that the OS and RFS of patients receiving second-line chemotherapy after first-line chemotherapy with GEM and platinum (GEM/CDDP or GEMOX) were 6.5−6.7 months and 1.9−3.2 months, respectively (*33-35*). The heterogeneous patient populations, small sample sizes, and lack of phase III trials were responsible for the absence of a standard second-line chemotherapy beyond the failure of GEM/CDDP treatment at this point.

In 2021, the ABC-06 phase III study indicated that 5-FU plus oxaliplatin (FOLFOX) chemotherapy could improve OS for patients with advanced biliary tract carcinoma after progression to first-line GEM/CDDP (*36*). A total of 162 patients were enrolled in that study, and the survival of patients receiving second-line FOLFOX chemotherapy (every 2 weeks for a maximum of 12 cycles) was significantly longer than that of the best supportive care group (median OS, 6.2 months *vs*. 5.3 months, $P = 0.031$), with a clinically meaningful increase in PFS (median, 4.0 months) and objective response (4.9%). That said, a higher rate of grade 3−5 adverse events was reported in the FOLFOX group (69.1% *vs*. 51.8%).

Phase II studies have evaluated the efficacy and safety of modified 5-FU plus oxaliplatin and irinotecan (FOLFIRINOX) as a second-line treatment for patients who failed to respond to GEM-based treatment for advanced biliary tract carcinoma. These studies indicated that the objective response rate was 10−26% with no complete response and that the median OS and PFS were 6.2−13.2 months and 2.8−6.7 months, respectively (*37-39*). FOLFIRINOX could be considered as an option for salvage treatment in these patients if long-term administration of modified FOLFIRINOX with toxicity management is possible.

Besides anticancer drugs, targeted therapies and precision medicine have been examined as a second-line treatment for patients with advanced biliary tract carcinoma (described below).

Table 2. Targeted therapy for biliary tract carcinoma (> 100 patients)

Author	Trial	Patient No.	Year	Regimen	Primary end point	Remarks	*Ref.*
Phase III trial							
Lee		268	2012	GEMOX/erlotinib *vs*. GEMOX	PFS		(*54*)
Abou-Alfa	ClarlDHy	185	2020	ivosidenib *vs*. placebo	PFS	IDH1 mutation	(*59*)
Phase II trial							
Bibeau	FIGHT-202	107	2022	pemigatinib (single arm)	NA	FGFR2 fusions	(*62*)
Tumor-agnostic therapy							
Hong		154	2020	larotrectinib (single arm)	NA	NTRK fusions	(*71*)
Demetri		121	2022	entrectinib (single arm)	NA	NTRK fusions	(*72*)

PFS, progression-free survival; GEMOX, gemcitabine plus oxaliplatin.

4. Adjuvant chemotherapy

Surgical resection is the only curative treatment for patients with biliary tract carcinoma, but these patients experience tumor recurrence at a high rate even after complete resection (*1*). Therefore, the efficacy of adjuvant therapy for biliary tract carcinoma should be verified (*40*).

Three phase III trials on adjuvant chemotherapy were conducted in the late 2010s. The phase III BILCAP study in 2019 compared oral capecitabine with observation as an adjuvant therapy in patients with biliary tract carcinoma after curative resection, and it provided evidence that capecitabine could improve the OS of these patients. Although the OS primary endpoint analyzed in the intention-to-treat analysis did not reach statistical significance (median OS: 51.1 months *vs*. 36.4 months; $P = 0.097$), the adjusted median OS was 53 months in the capecitabine group and 36 months in the observation group according to the per-protocol analysis ($P = 0.028$). Recurrence-free survival (RFS) of patients in the capecitabine group was also significantly longer than that of patients in the observation group (median RFS: 24.4 months *vs*. 17.5 months; $P = 0.033$) (*41*).

Alternatively, adjuvant GEMOX provided no benefit to patients undergoing curative resection for biliary tract carcinoma. In a phase III trial reported in 2019, both OS (median, 75.8 months *vs*. 50.8 months; $P = 0.74$) and RFS (30.4 months *vs*. 18.5 months; $P = 0.48$) did not differ significantly between the GEMOX group and the surveillance group (*42*).

Given that GEM/CDDP has been the standard first-line treatment for patients with unresectable biliary tract carcinoma as indicated in the ABC-02 trial (*7*), GEM/CDDP should be effective as adjuvant chemotherapy as well. A non-randomized small cohort phase II study indicated the promising survival of patients undergoing curative resection for biliary tract carcinoma (*43*). Moreover, a multicenter, open-label, randomized phase III trial on the efficacy of adjuvant GEM/CDDP is underway (*44*).

5. Targeted therapy

Targeted therapy is a type of personalized medical therapy that is designed to block specific molecules involved in the growth and spread of cancer cells. Interfering with a specific biochemical pathway kills cancer cells or keeps them from developing, growing, and spreading. Targeted therapy may cause less harm to normal cells and may cause fewer adverse reactions than other types of cancer treatment (Table 2).

5.1. Phase II trials using targeted therapy for biliary tract carcinoma

Phase II trials using targeted therapy for biliary tract carcinoma were reported from the late 2000s to the 2010s, but most of them failed to demonstrate the benefit of targeted therapies in cancer treatment with or without other anticancer drugs.

Lapatinib is an inhibitor of epidermal growth factor receptors (EGFRs) 1 and 2 and was administered to 17 patients with advanced biliary tract carcinoma (*45*). However, the response rate was 0%, indicating that treatment with lapatinib was not effective against biliary tract carcinoma. The addition of other molecularly targeted therapies to anticancer drugs did not enhance the activity of chemotherapy in patients with advanced biliary tract carcinoma. The phase II, randomized NCT00552149 study indicated that OS was 11.0 months in the GEMOX plus cetuximab group (cetuximab is an EGFR antagonist) and 12.4 months in the GEMOX alone group, and PFS was 6.1 months and 4.0 months, respectively (*46*). Sorafenib is a multi-kinase inhibitor drug and is the first drug that has demonstrated effectiveness against advanced hepatocellular carcinoma (*47*). First-line GEM plus sorafenib was evaluated in a double-blind phase II study (NCT00661830), but the addition of sorafenib to GEM did not result in improved efficacy in patients with advanced biliary tract carcinoma (median OS: 8.4 months [GEM plus sorafenib] *vs*. 11.2 months [GEM alone]; median PFS: 3.0 months *vs*. 4.9 months) (*48*). In a single-arm phase II study in 2018, the addition of a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab, to GEM/capecitabine did not improve outcomes for patients with advanced biliary tract carcinoma compared to

historical controls (response rate: 24%; median OS: 10.2 months; median PFS: 8.1 months) (*49*).

5.2. Erlotinib for biliary tract carcinoma

Erlotinib is an oral EGFR tyrosine-kinase inhibitor, and its most common and severe toxicity is a skin rash. The drug was approved for patients with various types of cancer such as pancreatic (*50*) and colorectal cancers (*51*), and in the late 2000s, phase II trials using erlotinib alone (*52*) or in combination with bevacizumab (*53*) indicated that the median OS and PFS in patients with advanced biliary tract carcinoma were 7.5−9.9 months and 2.6−4.4 months, respectively.

In the NCT01149122 phase III study in 2012, patients with advanced biliary tract carcinoma were assigned to receive either GEMOX or GEMOX plus erlotinib (*54*). This study noted no significant difference in either RFS (median: 4.2 months *vs*. 5.8 months, $P = 0.087$) or OS (9.5 months *vs*. 9.5 months, $P = 0.611$) between the GEMOX alone and GEMOX plus erlotinib groups. However, a subgroup analysis based on primary origin indicated the additional effect of erlotinib on PFS in patients with advanced cholangiocarcinoma (median: 3.0 months *vs*. 5.9 months, $P = 0.049$).

6. Precision medicine

With recent advances in biological technologies, high-throughput genome sequencing has been used to elucidate the genetic basis of many types of cancer. To date, next-generation sequencing (NGS) technologies have identified molecular targets, and genome-based drugs have been used clinically (*55,56*).

The US Food and Drug Administration (FDA) approved ivosidenib (for patients with *IDH1* mutation) and pemigatinib (for patients with *FGFR2* fusions/rearrangements or alterations) for patients with biliary tract carcinoma as a second-line chemotherapy. Both of these were well-tolerated and resulted in a favorable OS benefit.

6.1. Ivosidenib for biliary tract carcinoma with *IDH1* mutation

The Cancer Genome Atlas (TCGA) study that analyzed 38 intrahepatic cholangiocarcinoma samples found the *IDH1* mutation in seven samples (18.4%) of intrahepatic cholangiocarcinoma (*57*). Ivosidenib is a small molecule inhibitor of mutated *IDH1* that decreases the abnormal production of oncometabolite 2-hydroxyglutarate and that contributes to the differentiation of malignant cells (*58*).

The phase III randomized clinical ClarlDHy trial involved 187 patients with biliary tract carcinoma harboring the *IDH1* mutation who had disease progression after prior treatments (*59,60*). These patients were randomly assigned (2:1) to receive ivosidenib or a matched placebo. The PFS of the ivosidenib group (median, 2.7 months) was significantly longer than that of the placebo group (1.4 months, $P < 0.001$) (*59*). However, OS did not differ significantly between the two groups (median: 10.3 months *vs*. 7.5 months; $P = 0.09$). When adjusted for crossover, however, the median OS of the placebo group (5.1 months) was significantly shorter than that of the ivosidenib group ($P < 0.001$).

6.2. Pemigatinib to treat biliary tract carcinoma with *FGFR2* aberrations

In the TCGA study, RNA-seq data revealed that expressed *FGFR2* fusion/rearrangements were involved in the pathogenesis of cholangiocarcinoma. Pemigatinib is an oral *FGFR1*, *2*, *3* inhibitor that was first approved as a targeted treatment for biliary tract carcinoma by the US FDA in 2020.

The FIGHT-202 study – a multicenter, open-label, phase II study – included patients who had received first- or second-line systemic therapy for advanced biliary tract carcinoma. This study indicated that an objective response was achieved in 38 (35.5%) of 107 patients with *FGFR2* fusions/rearrangements treated with pemigatinib; a complete response was achieved in 3 (2.8%), a partial response was achieved in 35 (32.7), and 50 (46.7%) had stable disease (*61*). A follow-on study involved the same cohort was published two years later and it indicated that the median PFS was 7.0 months for patients with *FGFR2* fusions/rearrangements ($n = 65$) who received second-line pemigatinib during the trial (*62*). The phase III FIGHT-302 study comparing the efficacy of first-line pemigatinib *vs*. GEM/CDDP in patients with biliary tract carcinoma with *FGFR2* fusions/rearrangements is ongoing (*63*).

7. Tumor-agnostic treatment

Due to the direct detection of gene fusion using the NGS approach, *NTRK* fusion assessment has recently become a standard part of management for patients with diverse types of advanced cancers (*64*), although the frequency of *NTRK* fusions in biliary tract carcinoma is estimated to be 0.25−3.6% (*65,66*). Gene fusions involving *NTRK1*, *NTRK2*, or *NTRK3* were found in a broad range of pediatric and adult malignancies (*67,68*), leading to the expression of chimeric rearrangements in tropomyosin receptor kinases (*TRKs*). Entrectinib and larotrectinib are inhibitors of *TRKA*, *B*, and *C*, and have been shown to have prominent anti-tumor activity against oncogenic *NTRK* gene fusion-positive solid tumors including biliary tract carcinoma (*69,70*).

In 2020, a pooled study of larotrectinib for *TRK* fusion-positive advanced solid tumors (NAVIGATE), including biliary tract carcinoma, indicated that an objective response was achieved in 121 (79.0%) of 153

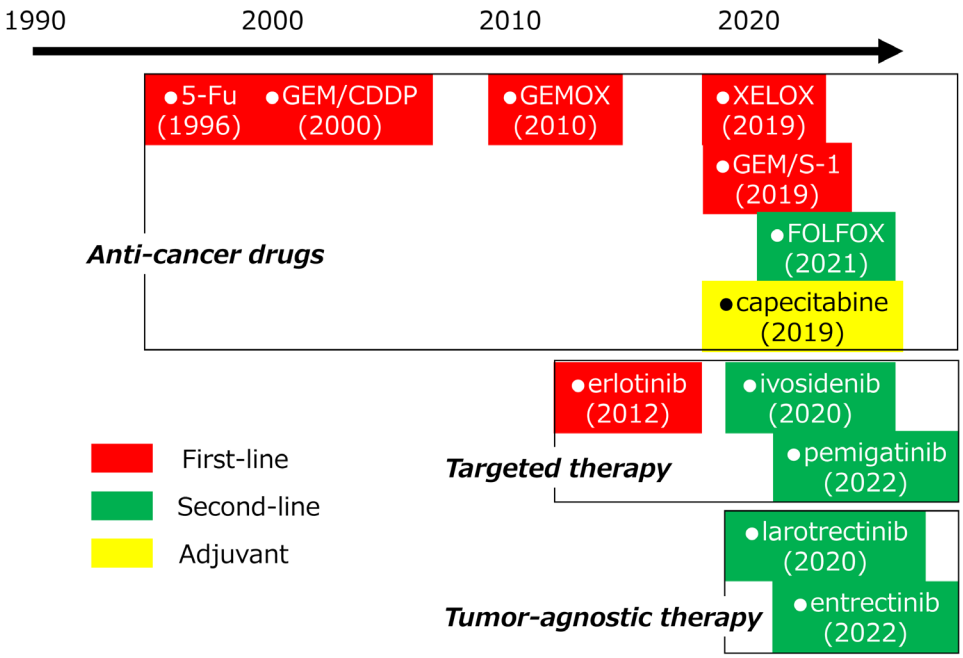

Figure 1. The history of treatment for biliary tract carcinoma.

patients while a complete response was achieved in 24 (15.6%) (*71*). Moreover, integrated analysis using the datasets of three ongoing clinical trials of entrectinib (ALKA-372-001 [phase I], STARTRK-1 [phase I], and STARTRK-2 [phase II]) was performed in 2022. This pre-specified analysis of 121 adult patients with advanced *NTRK* fusion-positive solid tumors included 1 patient with biliary tract carcinoma. An objective response was achieved in 74 patients (61.2%), including a complete response in 19 (15.7%), a partial response in 55 (45.5%), and stable disease in 13 (10.7%). At the data cut-off, OS and PFS were 33.8 months and 13.8 months, respectively (*72*).

8. Immunotherapy

Checkpoint inhibitors are monoclonal antibodies targeting the cytotoxic T lymphocyte antigen 4 or PD-1/PD-L1 immune checkpoint pathways, which block a signaling pathway that prevents the activation of T cells from attacking the cancer and enable tumor-reactive T-cells to mount an anticancer immune response (*73*). In 2017, the US FDA approved the anti-PD-1 agent pembrolizumab for the treatment of any type of cancer with microsatellite instability-high (MSI-H) (*74*). However, no studies have indicated the efficacy of immune checkpoint inhibitors for advanced biliary tract carcinoma thus far (*75,76*).

Immunotherapy for biliary tract carcinoma has now been explored and is currently being evaluated in several clinical trials to provide novel and more effective treatment options. A randomized phase II IMbrave 151 study (atezolizumab + GEM/CDDP in combination with or without bevacizumab) is now underway, and that regimen is expected to be effective as a first-line treatment for advanced biliary tract carcinoma (*77*).

9. Future perspectives

After the establishment of a first-line treatment using GEM/CDDP or GEM/S-1 regimen for advanced biliary tract carcinoma, the next era will witness the identification of biomarkers that determine subtypes of patients who are amenable to precision medicine (Figure 1). Due to the easy access to cancer panels, the presence of driver mutations, such as *IDH1*, and fusion events, such as the *FGFR2* and *TRK* genes in biliary tract carcinoma, and MSI-H in all types of solid tumors can easily be determined. Hence, the personalized treatment options for patients with advanced biliary tract carcinoma are steadily increasing. However, such precision medicine is still limited to only a minority of patients receiving treatment for biliary tract carcinoma. However, clinical trials of immune checkpoint inhibitors in combination with or without other anticancer drugs are currently underway, and immunotherapy options for biliary tract carcinoma are a current topic of debate. Data from these clinical trials should lead to more effective treatment options for this immunologically "cold" malignancy.

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