



Optimum chemotherapy for the management of advanced biliary tract cancer

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many chemotherapeutic regimens and targeted therapies for the treatment of BTC, the standard of care for advanced BTC remains the combination of gemcitabine with cisplatin. Many new molecules targeting proliferation and survival pathways, the immune response and angiogenesis are currently undergoing phase I and II trials for the treatment of advanced BTC with promising results.

Key words: Biliary tract cancer; Chemotherapy; Updates; Treatment modalities; Novel therapies

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Core tip: This paper is a recent study outlining the most recent updates on the treatment of advanced biliary tract cancers. After a brief review of the different treatments used for advanced biliary tract cancers, current treatment options, novel therapies and future approaches are discussed.

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Abstract

Biliary tract cancers (BTCs) are highly fatal malignancies, which are often diagnosed at an advanced stage and have relatively poor prognosis. The treatment of patients with advanced BTC is systemic, based on chemotherapy or best supportive care, depending on their performance status. Despite clinical trials studying

INTRODUCTION

Biliary tract cancers (BTCs) are orphan, heterogeneous and highly fatal malignancies that represent less than 1% of all cancers including gallbladder cancer (GBC), cholangiocarcinoma (CC) and cancers of the ampulla of Vater (CAV). CAV are excluded from this review because of their different characteristics and better prognosis.

Of the two other BTCs, GBC is two times more frequent than CC, and between the two known CC subtypes, the extra-hepatic subtype is more common than intra-hepatic CC (15%). Moreover, the incidence of intra-hepatic CC is increasing in different countries (United States, United Kingdom and Australia), but its cause has not yet been elucidated^[1].

These cancers are often diagnosed at an advanced stage defined as unresectable disease (metastatic or locally advanced) due to their nonspecific symptomatology, and they are associated with relatively poor prognosis. Five-year survival rates are 5%-10% for GBC and 10%-40% for CC^[2].

Given its rarity and diversity, few clinical trials have studied optimum treatment for BTC. Historically, there has been no standard treatment for neither advanced (defined as stage IVA) nor metastatic BTC (defined as stage IVB). Treatments for these cancers have been extrapolated from treatment regimens for metastatic pancreatic cancer. However, as of 2010, many new trials have been designed to achieve optimum chemotherapeutic treatment for advanced BTC.

EVOLUTION OF TREATMENT MODALITIES

BTC studies between 1985 and 2006 have enrolled small numbers of patients (5-65 patients) but were limited by heterogeneity. Only three studies were randomized, including two phase II trials^[3,4] and one phase III trial^[5].

In 2007, Eckel *et al*^[6] attempted to pioneer a chemotherapy standard of care for BTC. This group published a pooled analysis of 104 clinical trials that regrouped greater than 2800 patients and evaluated different treatment modalities. This pooled analysis suggested that the combination of gemcitabine and cisplatin or oxaliplatin is the most active regimen. Therefore, this modality was considered a provisional standard regimen for BTC until a new evidence-based standard was defined.

The first large randomized study (81 patients) was an Indian monocentric series that exclusively included GBC. This study compared the best supportive care (BSC) to 5-FU and folinic acid (FUFA) and modified gemcitabine and oxaliplatin. The results demonstrated improved overall survival (OS) and progression-free survival (PFS) with GEMOX compared with BSC and FUFA in unresectable GBC^[7].

The British United Kingdom ABC-02 trial is the largest published trial designed for BTC. This study enrolled 410 patients and compared gemcitabine with its combination with cisplatin. The latter was associated with a significant survival advantage without adverse substantial toxicity. Thus, this regimen was considered an appropriate treatment option for patients with advanced BTC^[8]. Another Japanese trial confirmed this conclusion. This study also showed

Table 1 Single-agent targeted therapies in phase II trials for advanced biliary tract cancer

Ref.	Line	N	Target	Treatment	RR (%)	PFS	OS
Philip <i>et al</i> ^[12] 2006	1-2	42	EGFR	Erlotinib	8	2.6	7.5
Costello <i>et al</i> ^[13] 2009	1-3	20	Proteasome	Bortezomib	0	1.5	9.5
Ramanathan <i>et al</i> ^[14] 2009	1-2	17	EGFR, HER2	Lapatinib	0	1.8	5.2
Buzzoni <i>et al</i> ^[15] 2010	2	18	mTOR	Everolimus	6	NA	NA
Bengala <i>et al</i> ^[16] 2010	1-5	46	VEGF, BRAF	Sorafenib	2	2.3	4.4
El Khoueiry <i>et al</i> ^[17] 2011	1	31	VEGF, BRAF	Sorafenib	0	3.0	9.0
Bekaii-Saab <i>et al</i> ^[18] 2011	1-2	28	MEK1-2	Selumetinib	12	3.7	9.8
Yi <i>et al</i> ^[19] 2012	2	56	VEGF	Sunitinib	8.9	1.7	NA

N: Number of participants; NA: Not available; OS: Overall survival; PFS: Progression-free survival; RR: Response rate.

that GBC has a poorer prognosis compared with non-GBC with a median OS of 9.1 mo for GBC and 13 mo for non-GBC^[9]. A recent meta-analysis of these two studies recommended the combination of gemcitabine and cisplatin as a standard of care for the first-line treatment of advanced BTC for patients with good PS^[10].

A Japanese phase II trial associating S1 with gemcitabine demonstrated a better response rate compared with gemcitabine alone, but the superiority of this combination therapy was not completely clear^[11].

With the era of targeted therapies, many strategies have been considered for BCT treatment. Single-agent or combined targeted therapies and chemotherapy combinations were the available options. The most frequent mutations targeted in these cancers include those in EGFR, Her2, KRAS and BRAF.

Since 2006, multiple phase II trials have studied single-agent or combined targeted therapies. Studied have included erlotinib^[12], bortezomib^[13], lapatinib^[14], everolimus^[15], sorafenib^[16,17], selumetinib^[18], and sunitinib^[19] and the combinations erlotinib and bevacizumab^[20] and sorafenib and erlotinib^[21]. All of the corresponding trials were negative (Table 1).

The association between targeted therapy and chemotherapy was also evaluated. Many clinical trials have evaluated the combination of a targeted therapeutic agent with the standard of care, which is gemcitabine plus cisplatin or oxaliplatin. The combination of gemcitabine and oxaliplatin with bevacizumab revealed a response rate (RR) of 40%, PFS of 7.0 mo and OS of 12.7 mo^[22].

Adding an anti-EGFR drug (cetuximab, erlotinib and panitumumab) to gemcitabine and oxaliplatin was studied in several phase II and III trials. A phase II study of 30 patients testing the association between gemcitabine, oxaliplatin and cetuximab in

advanced or metastatic BTC showed an objective RR of 63%^[23]. These results were confirmed in a French-German phase II randomized trial (BINGO) that evaluated the addition of cetuximab to the combination of gemcitabine and oxaliplatin. The RR overcame the 60% barrier in the first four months after adding cetuximab. The PFS and OS were not significantly different between the two concerned arms^[24]. A randomized phase III trial studied the addition of erlotinib to gemcitabine and oxaliplatin; the PFS increase observed with erlotinib was not statistically significant, and the OS was the same for the two groups. In subgroup analyses, the PFS was only significantly increased in the CC group. In a phase II marker-driven trial of panitumumab and GEMOX followed by capecitabine for seven days for KRAS wild-type BTC, the results met the efficacy criteria for future testing in a randomized trial with a RR of 33%, PFS of 8.3 mo and OS of 10 mo^[25]. All of the studies evaluating the addition of anti-EGFR to GEMOX in BTC failed to approve this combination as a standard of care.

The association between gemcitabine, the most effective chemotherapy for BTC, and MEK inhibitors, which showed an acceptable response, could be considered a perfect combination if it were not for their antagonist effects. A recent study revealed this combination as highly schedule-dependent with better results when these two drugs are used sequentially rather than simultaneously^[26].

CURRENT TREATMENT OPTIONS

Despite evaluating many chemotherapeutic regimens and targeted therapies for the treatment of BTC, the standard of care for advanced BTC remains the combination of gemcitabine with cisplatin^[8]. A regimen of gemcitabine and 5-FU is an acceptable option under some circumstances^[27]. In the particular case of Klatskin tumors, aggressive surgery may be performed in a curative perspective. Effective, liver and portal vein resections are recommended for selected patients with advanced Klatskin tumors^[28]. In general, the BSC is possible for patients with poor PS. OS with the standard of care is less than one year. Therefore, enrolling patients in clinical trials is recommended.

NOVEL THERAPIES AND APPROACHES

Many new concepts for treating advanced BTC are being evaluated, including angiogenesis inhibition, targeting tyrosine kinase signaling cascade components, manipulating the stromal reaction, the immune response, oncofetal signaling and epigenetic modifications^[27].

Immunotherapy and vaccination

Immunotherapy in cancer has moved forward during the last few years, and several regimens have been approved as a standard of care for different cancers

e.g., ipilimumab for melanoma.

BTC has been reported to express a variety of tumor-associated antigens, such as Wilms' tumor gene 1 and mucin 1, which could be potential targets for immunotherapies^[29-31]. Several clinical trials for immunotherapies targeting these molecules have been recently reported with promising results^[32,33].

Inhibition of angiogenesis

After the failure of many trials evaluating anti-angiogenic drugs for the management of BTC, axitinib (AG-013736), an oral specific VEGFR TKI, shows potential therapeutic utility for vascular endothelial growth factor-expressing CCs^[34].

Targeting signaling pathways

IFG1R, MEK, PI3K, AKT, and mTOR are the most frequent signaling pathway targets evaluated for the treatment of advanced BTC.

A phase I study evaluating a MEK inhibitor (MEK162) showed an acceptable safety profile and desirable pharmacokinetics properties at 60 mg BID, and RECIST responses were observed in patients with BTC^[35].

Everolimus (RAD001) exhibits multiple effects mediated by the inhibition of mTOR and may serve as a promising agent for the treatment of CC^[36].

CONCLUSION

Despite numerous trials evaluating the chemotherapeutic regimens and targeted therapies for BTC, the combination of gemcitabine and cisplatin remains the gold standard for the treatment of BTC. At this time, OS is less than one year, and enrolling patients in clinical trials is also recommended. New strategies should be adopted for the management of BTC. As the molecular biology and genetic origin of this cancer improves and becomes completely elucidated, perhaps personalized therapy will achieve better outcomes. Subsequently, individualized treatments may be established according to molecular profiles and epigenetics with targeted and immunotherapies.

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