

Optimum chemotherapy for the management of advanced biliary tract cancer

Marwan Ghosn, Hampig Raphael Kourie, Elie El Rassy, Ralph Chebib, Fadi El Karak, Colette Hanna, Dolly Nasr

Marwan Ghosn, Hampig Raphael Kourie, Elie El Rassy, Ralph Chebib, Fadi El Karak, Colette Hanna, Dolly Nasr, Department of Oncology, Faculty of Medicine, Saint Joseph University, Beirut 2038 3054, Lebanon

Author contributions: Ghosn M initiated the review; Ghosn M, Kourie HR, El Rassy E performed the review, analyzed the data and wrote first draft; Ghosn M, Kourie HR, El Rassy E, Chebib R, El Karak F, Hanna C and Nasr D reviewed and commented on the paper and provided final approval.

Conflict-of-interest: To the best of our knowledge, no conflict of interest exists.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Marwan Ghosn, MD, Department of Oncology, Faculty of Medicine, Saint Joseph University, Monot St, Beirut, PO Box 166830, Beirut 2038 3054, Lebanon. mghosn.hdf@usj.edu.lb

Telephone: +961-1-3226842

Fax: +961-1-1613397

Received: November 30, 2014

Peer-review started: November 30, 2014

First decision: December 26, 2014

Revised: January 13, 2015

Accepted: February 13, 2015

Article in press: February 13, 2015

Published online: April 14, 2015

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

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Ghosn M, Kourie HR, El Rassy E, Chebib R, El Karak F, Hanna C, Nasr D. Optimum chemotherapy for the management of advanced biliary tract cancer. *World J Gastroenterol* 2015; 21(14): 4121-4125 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i14/4121.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i14.4121>

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.

REFERENCES

- 1 **Rajagopalan V**, Daines WP, Grossbard ML, Kozuch P. Gallbladder and biliary tract carcinoma: A comprehensive update, Part 1. *Oncology* (Williston Park) 2004; **18**: 889-896 [PMID: 15255172]
- 2 **de Groen PC**, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. *N Engl J Med* 1999; **341**: 1368-1378 [PMID: 10536130 DOI: 10.1056/NEJM199910283411807]
- 3 **Kornek GV**, Schuell B, Laengle F, Gruenberger T, Penz M, Karall K, Depisch D, Lang F, Scheithauer W. Mitomycin C in combination with capecitabine or biweekly high-dose gemcitabine in patients with advanced biliary tract cancer: a randomised phase II trial. *Ann Oncol* 2004; **15**: 478-483 [PMID: 14998852]
- 4 **Ducreux M**, Van Cutsem E, Van Laethem JL, Gress TM, Jeziorski K, Rougier P, Wagener T, Anak O, Baron B, Nordlinger B. A randomised phase II trial of weekly high-dose 5-fluorouracil with and without folinic acid and cisplatin in patients with advanced biliary tract carcinoma: results of the 40955 EORTC trial. *Eur*

- J Cancer* 2005; **41**: 398-403 [PMID: 15691639 DOI: 10.1016/j.ejca.2004.10.026]
- 5 **Rao S**, Cunningham D, Hawkins RE, Hill ME, Smith D, Daniel F, Ross PJ, Oates J, Norman AR. Phase III study of 5FU, etoposide and leucovorin (FELV) compared to epirubicin, cisplatin and 5FU (ECF) in previously untreated patients with advanced biliary cancer. *Br J Cancer* 2005; **92**: 1650-1654 [PMID: 15856037 DOI: 10.1038/sj.bjc.6602576]
 - 6 **Eckel F**, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. *Br J Cancer* 2007; **96**: 896-902 [PMID: 17325704 DOI: 10.1038/sj.bjc.6603648]
 - 7 **Sharma A**, Dwary AD, Mohanti BK, Deo SV, Pal S, Sreenivas V, Raina V, Shukla NK, Thulkar S, Garg P, Chaudhary SP. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. *J Clin Oncol* 2010; **28**: 4581-4586 [PMID: 20855823 DOI: 10.1200/JCO.2010.29.3605]
 - 8 **Valle J**, Wasan H, Palmer DH, Cunningham D, Anthony A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010; **362**: 1273-1281 [PMID: 20375404 DOI: 10.1056/NEJMoa0908721]
 - 9 **Okusaka T**, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, Nagino M, Kondo S, Nagaoka S, Funai J, Koshiji M, Nambu Y, Furuse J, Miyazaki M, Nimura Y. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer* 2010; **103**: 469-474 [PMID: 20628385 DOI: 10.1038/sj.bjc.6605779]
 - 10 **Valle JW**, Furuse J, Jitlal M, Beare S, Mizuno N, Wasan H, Bridgewater J, Okusaka T. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol* 2014; **25**: 391-398 [PMID: 24351397 DOI: 10.1093/annonc/mdt540]
 - 11 **Sasaki T**, Isayama H, Nakai Y, Ito Y, Yasuda I, Toda N, Kogure H, Hanada K, Maguchi H, Sasahira N, Kamada H, Mukai T, Okabe Y, Hasebe O, Maetani I, Koike K. A randomized phase II study of gemcitabine and S-1 combination therapy versus gemcitabine monotherapy for advanced biliary tract cancer. *Cancer Chemother Pharmacol* 2013; **71**: 973-979 [PMID: 23355041 DOI: 10.1007/s00280-013-2090-4]
 - 12 **Philip PA**, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, Donehower RC, Fitch T, Picus J, Erlichman C. Phase II study of erlotinib in patients with advanced biliary cancer. *J Clin Oncol* 2006; **24**: 3069-3074 [PMID: 16809731 DOI: 10.1200/JCO.2005.05.3579]
 - 13 **Costello MR**, Meropol NJ, Denlinger CS, Engstrom PF, Wright JJ, Li T, McLaughlin S, Beard M, Cimildoro R, Cohen SJ. A phase II trial of the proteasome inhibitor bortezomib in patients with recurrent or metastatic adenocarcinoma of the bile duct or gallbladder (NCI #6135). *J Clin Oncol* 2009; **27** suppl: e15605
 - 14 **Ramanathan RK**, Belani CP, Singh DA, Tanaka M, Lenz HJ, Yen Y, Kindler HL, Iqbal S, Longmate J, Mack PC, Lurje G, Gandour-Edwards R, Dancy J, Gandara DR. A phase II study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. *Cancer Chemother Pharmacol* 2009; **64**: 777-783 [PMID: 19169683 DOI: 10.1007/s00280-009-0927-7]
 - 15 **Buzzoni R**, Pusceddu S, Platania M, Barone G, Valente M, Di Guardo L, Bajetta E. Efficacy and safety of RAD001 in advanced biliary tract cancer (BTC) patients (pts) progressing after first-line chemotherapy: A phase II study. *ASCO Meet Abstr* 2010; **28** (15_suppl): e14500
 - 16 **Bengala C**, Bertolini F, Malavasi N, Boni C, Aitini E, Dealis C, Zironi S, Depenni R, Fontana A, Del Giovane C, Luppi G, Conte P. Sorafenib in patients with advanced biliary tract carcinoma: a phase II trial. *Br J Cancer* 2010; **102**: 68-72 [PMID: 19935794 DOI: 10.1038/sj.bjc.6605458]
 - 17 **El-Khoueiry AB**, Rankin CJ, Ben-Josef E, Lenz HJ, Gold PJ, Hamilton RD, Govindarajan R, Eng C, Blanke CD. SWOG 0514: a phase II study of sorafenib in patients with unresectable or metastatic gallbladder carcinoma and cholangiocarcinoma. *Invest New Drugs* 2012; **30**: 1646-1651 [PMID: 21748296 DOI: 10.1007/s10637-011-9719-0]
 - 18 **Bekaii-Saab T**, Phelps MA, Li X, Saji M, Goff L, Kauh JS, O'Neil BH, Balsom S, Balint C, Lierseemann R, Vasko VV, Bloomston M, Marsh W, Doyle LA, Ellison G, Grever M, Ringel MD, Villalona-Calero MA. Multi-institutional phase II study of selumetinib in patients with metastatic biliary cancers. *J Clin Oncol* 2011; **29**: 2357-2363 [PMID: 21519026 DOI: 10.1200/JCO.2010.33.9473]
 - 19 **Yi JH**, Thongprasert S, Lee J, Doval DC, Park SH, Park JO, Park YS, Kang WK, Lim HY. A phase II study of sunitinib as a second-line treatment in advanced biliary tract carcinoma: a multicentre, multinational study. *Eur J Cancer* 2012; **48**: 196-201 [PMID: 22176869 DOI: 10.1016/j.ejca.2011.11.017]
 - 20 **Lubner SJ**, Mahoney MR, Kolesar JL, Loconte NK, Kim GP, Pitot HC, Philip PA, Picus J, Yong WP, Horvath L, Van Hazel G, Erlichman CE, Holen KD. Report of a multicenter phase II trial testing a combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer: a phase II Consortium study. *J Clin Oncol* 2010; **28**: 3491-3497 [PMID: 20530271 DOI: 10.1200/JCO.2010.28.4075]
 - 21 **El-Khoueiry AB**, Rankin C, Siegel AB, Iqbal S, Gong IY, Micetich KC, Kayaleh OR, Lenz HJ, Blanke CD. S0941: a phase 2 SWOG study of sorafenib and erlotinib in patients with advanced gallbladder carcinoma or cholangiocarcinoma. *Br J Cancer* 2014; **110**: 882-887 [PMID: 24423918 DOI: 10.1038/bjc.2013.801]
 - 22 **Zhu AX**, Meyerhardt JA, Blaszkowsky LS, Kambadakone AR, Muzikansky A, Zheng H, Clark JW, Abrams TA, Chan JA, Enzinger PC, Bhargava P, Kwak EL, Allen JN, Jain SR, Stuart K, Horgan K, Sheehan S, Fuchs CS, Ryan DP, Sahani DV. Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome: a phase 2 study. *Lancet Oncol* 2010; **11**: 48-54 [PMID: 19932054 DOI: 10.1016/S1470-2045(09)70333-X]
 - 23 **Gruenberger B**, Schueller J, Heubrandtner U, Wrba F, Tamandl D, Kaczirek K, Roka R, Freimann-Pircher S, Gruenberger T. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *Lancet Oncol* 2010; **11**: 1142-1148 [PMID: 21071270 DOI: 10.1016/S1470-2045(10)70247-3]
 - 24 **Malka D**, Cervera P, Heurteau-Foulon S, Wendum D, Trarbach T, De La Fouchardiere C, Boucher E, Fartoux L, Faivre S, Pignon JP, Rosmorduc O, Giret F. Gemcitabine and oxaliplatin (GEMOX) alone or with cetuximab in first-line treatment of advanced biliary cancers (ABC): Exploratory analyses according to tumor KRAS/BRAF mutations and EGFR expression in a randomized phase II trial (BINGO). *ASCO Meet Abstr* 2013; **31** (15_suppl): 4127
 - 25 **Jensen LH**, Lindebjerg J, Ploen J, Hansen TF, Jakobsen A. Phase II marker-driven trial of panitumumab and chemotherapy in KRAS wild-type biliary tract cancer. *Ann Oncol* 2012; **23**: 2341-2346 [PMID: 22367707 DOI: 10.1093/annonc/mds008]
 - 26 **Xu J**, Knox JJ, Ibrahimov E, Chen E, Serra S, Tsao M, Cao P, Vines D, Green DE, Metran-Nascente C, McNamara MG, Hedley DW. Sequence dependence of MEK inhibitor AZD6244 combined with gemcitabine for the treatment of biliary cancer. *Clin Cancer Res* 2013; **19**: 118-127 [PMID: 23091117 DOI: 10.1158/1078-0432.CCR-12-2557]
 - 27 **Hezel AF**, Zhu AX. Systemic therapy for biliary tract cancers. *Oncologist* 2008; **13**: 415-423 [PMID: 18448556 DOI: 10.1634/theoncologist.2007-0252]
 - 28 **Nimura Y**, Hayakawa N, Kamiya J, Maeda S, Kondo S, Yasui A, Shionoya. Combined portal vein and liver resection for carcinoma of the biliary tract. *British J Surg* 1991; **78**: 727-731 [DOI: 10.1002/bjs.1800780629]
 - 29 **Nakatsuka S**, Oji Y, Horiuchi T, Kanda T, Kitagawa M, Takeuchi T, Kawano K, Kuwae Y, Yamauchi A, Okumura M, Kitamura Y, Oka Y, Kawase I, Sugiyama H, Aozasa K. Immunohistochemical detection of WT1 protein in a variety of cancer cells. *Mod Pathol* 2006; **19**: 804-814 [PMID: 16547468 DOI: 10.1038/modpathol.3800588]

- 30 **Higashi M**, Yonezawa S, Ho JJ, Tanaka S, Irimura T, Kim YS, Sato E. Expression of MUC1 and MUC2 mucin antigens in intrahepatic bile duct tumors: its relationship with a new morphological classification of cholangiocarcinoma. *Hepatology* 1999; **30**: 1347-1355 [PMID: 10573510 DOI: 10.1002/hep.510300609]
- 31 **Mall AS**, Tyler MG, Ho SB, Krige JE, Kahn D, Spearman W, Myer L, Govender D. The expression of MUC mucin in cholangiocarcinoma. *Pathol Res Pract* 2010; **206**: 805-809 [PMID: 20947262 DOI: 10.1016/j.prp.2010.08.004]
- 32 **Kaida M**, Morita-Hoshi Y, Soeda A, Wakeda T, Yamaki Y, Kojima Y, Ueno H, Kondo S, Morizane C, Ikeda M, Okusaka T, Takaue Y, Heike Y. Phase I trial of Wilms tumor 1 (WT1) peptide vaccine and gemcitabine combination therapy in patients with advanced pancreatic or biliary tract cancer. *J Immunother* 2011; **34**: 92-99 [PMID: 21150717 DOI: 10.1097/CJI.0b013e3181fb65b9]
- 33 **Shimizu K**, Kotera Y, Aruga A, Takeshita N, Takasaki K, Yamamoto M. Clinical utilization of postoperative dendritic cell vaccine plus activated T-cell transfer in patients with intrahepatic cholangiocarcinoma. *J Hepatobiliary Pancreat Sci* 2012; **19**: 171-178 [PMID: 21874278 DOI: 10.1007/s00534-011-0437-y]
- 34 **Takahashi H**, Ojima H, Shimizu H, Furuse J, Furukawa H, Shibata T. Axitinib (AG-013736), an oral specific VEGFR TKI, shows potential therapeutic utility against cholangiocarcinoma. *Jpn J Clin Oncol* 2014; **44**: 570-578 [PMID: 24755544 DOI: 10.1093/jjco/hyu045]
- 35 **Finn RS**, Javle MM, Tan BR, Weekes CD, Bendell JC, Patnaik A, Naaz Khan G, Laheru D, Anderson L, Christy-Bittel JL, Barrett E, Guthrie G, Litwiler K, Bekaii-Saab T. A phase I study of MEK inhibitor MEK162 (ARRY-438162) in patients with biliary tract cancer. *J Clin Oncol* 2012; **30** suppl 4: abstr 220
- 36 **Moolthiya P**, Tohtong R, Keeratichamroen S, Leelawat K. Role of mTOR inhibitor in cholangiocarcinoma cell progression. *Oncol Lett* 2014; **7**: 854-860 [PMID: 24527093 DOI: 10.3892/ol.2014.1799]

P- Reviewer: Kaiser GM **S- Editor:** Qi Y **L- Editor:** A
E- Editor: Zhang DN





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045