

Brief Commentary

ERBB and FGFR2 pathway inhibition in biliary tract cancers – Dawn of a new beginning

Amol Patel¹, Manoj Prashar²

¹Oncology centre, INHS Asvini, Mumbai, ²Malignant Diseases Treatment Centre, Command Hospital, Pune, Maharashtra, India.



*Corresponding author:

Amol Patel, MD, DM,
Assistant Professor, Oncology
Centre, INHS Asvini, Near RC
Church, Mumbai, Maharashtra,
India

dr.amolpatel@hotmail.com.

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Biliary tract cancers (BTCs) have varied and unique incidence pattern and it has increasing trend. In some part of the world, these are the most common cancers. Cholangiocarcinoma (CCA) is the most common cancer in Thailand (northeast region) with age standardized rate (ASR) per 100,000 populations of 85 and it is least common in Europe (ASR <2) and the United States (ASR 2.2).^[1] Interestingly, incidence varies in different parts of the country. In Thailand's northeast region, it is the most common as mentioned, ASR is 14.5 and 5.7 in North-Central and South region, respectively. Similarly, gallbladder cancer (GBC) has varied incidence pattern across in India. In northern states of India, it is the most common and in southern states it is the least common.^[2,3]

Rarity in Western world precluded BTCs from research in field of targeted and molecular therapies. The prognosis of GBC has not changed in the past 20 years.^[4] Gemcitabine with cisplatin or oxaliplatin remained the standard of choice of treatment in metastatic BTCs as first-line setting and there is no established second-line therapy available till date.^[5,6] CCA is classified as intrahepatic (iCCA), perihilar (pCCA), and distal CCA (dCCA). CCA and GBC are treated altogether in clinical trials considering their anatomical location, physiological common functions, and clinical presentations. Comprehensive genomic profiling of tumors has lead to better understanding of aberrant and newer molecular pathways in biliary tract cancers.^[7]

Recent FDA approval of pemigatinib, a selective, oral, and potent fibroblast growth factor receptor (FGFR) 1, 2, and 3 inhibitor, in metastatic CCA with FGFR2 gene fusion or rearrangement brought first targeted therapy to biliary world of cancers.^[8] This approval was based on multicenter, single-arm, Phase 2 study lead by Abou-Alfa *et al.*^[9] Simultaneously, Foundation Medicine CDx also got approval for companion diagnostic test for the detection of FGFR fusion or rearrangement. This FIGHT-202, multicohort study enrolled 146 patients, out of which 107 had FGFR2 fusion or rearrangements. Twenty patients had other FGFR genetic alterations. All patients received at least one line of systemic therapy. Pemigatinib was administered at a dose of 13.5 mg orally (2 weeks on, 1 week off).

Primary end point was objective response which included confirmed overall response and partial response. Objective response was 35.5%. Three patients had complete response and 35 patients had partial response. These responses were seen exclusively in FGFR2 fusion or rearrangement. There were no responses seen in patients with other or no FGF/FGFR alterations, highlighting the importance of testing and treating only patients with FGFR2 fusion or rearrangement.

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Table 1: FGFR and ERBB gene aberrations in biliary tract cancers.

Molecular characteristics	Intrahepatic cholangiocarcinoma		Extrahepatic cholangiocarcinoma		Gallbladder cancer			
	Mondaca <i>et al.</i> ^[12] (n=313) (%)	Ross <i>et al.</i> ^[11] (n=412) (%)	Mondaca <i>et al.</i> ^[12] (n=93) (%)	Ross <i>et al.</i> ^[11] (n=57) (%)	Nakamura <i>et al.</i> ^[10] (%)	Mondaca <i>et al.</i> ^[12] (n=111) (%)	Ross <i>et al.</i> ^[11] (n=85) (%)	Patel <i>et al.</i> ^[13] (n=50) (%)
ERBB2 #	2.2	4	7.5	11	-	12.6	16	12
Ampli	-	-	-	-	-	0.01 (2/111)	-	6
Mut+ampli	-	-	-	-	-	-	-	-
ERBB3	-	-	-	-	-	-	-	4
Ampli	-	-	-	-	-	-	-	6
Mut	-	-	-	-	-	-	-	8
ERBB1	4#	-	-	-	-	-	-	8
ERBB4	4	-	-	-	-	-	-	8
FGFR1 mutation	-	-	-	-	-	-	-	4
FGFR2 mutation	4	-	-	-	-	-	-	0
FGFR3 mutation	-	-	-	-	-	-	-	6
FGFR4 mutation	-	-	-	-	-	-	-	2
FGFR3 amplification	-	-	-	-	-	-	-	2
FGFR3	-	-	-	-	-	-	-	-
rearrangement	-	11**	-	0	0	-	3	2* (1/50)
FGFR2 fusion/rearrangement	-	5.5 (6/109)	-	-	0	-	-	-

(-) data are limited by molecular complexity and availability. FGFR1 mutations – R22S, D432N, I379V, N65K, *FGFR2 amplification and FGFR2-PLEKHA1 rearrangement. Patient had GB neck mass. FGFR2 mutations – A461P, C382R, FGFR3 mutations – NIL, FGFR4 mutations – R154C, A553V, V109I. ERBB mutation was seen in 12 patients. #Missense mutations (unknown significance). **All FGFR aberrations combined

Hyperphosphatemia was the most common adverse effect (60%) and hypophosphatemia occurred in 23% of patients. About 9% of patients discontinued treatment and no death was attributed to pemigatinib as assessed by the investigators. Objective responses of 35% and median duration of treatment of 7.2 months in second-line setting are noteworthy and this success in CCA has brought a new hope to the patients and scientific community treating these diseases.

As disease incidence is varied, the molecular aberrations also differ in frequency as per site of BTC.^[10-12] Frequency of FGFR and ERBB genomic aberrations as per site is depicted in Table 1. GBC has unique molecular aberrations. We did comprehensive genomic profiling of metastatic GBC in 50 patients and treated patients with targeted treatment in second-line setting.^[13] Das *et al.* studied the role of anti-Her2neu-directed therapy in GBC which is Her2neu amplified in 17%. There are encouraging results with 71.4% of overall response rate, 9.7 months of Median PFS and 14 months Median OS in 30 patients. Trastuzumab was combined with first-/second-line chemotherapy regimens.^[14] These data were published at ASCO 2020 in abstract form. ERBB2 amplification and/or mutation are more common in GBC than CCA. The presence of EGFR and FGFR mutations is conferring to resistance to targeted therapy which is the matter of active research. We found encouraging response to addition of lapatinib to trastuzumab plus chemotherapy in ERBB2-mutated GBC.^[13] ERBB2 mutations in breast cancer and GBC are 2% and 30%, respectively. Comprehensive genomic profiling not only improved our understanding of molecular pathways but also the possible underlying resistance mechanisms.

These promising results are opening the gates for Phase 2 and 3 trials in BTCs. Multiple clinical trials of targeted therapy and immunotherapy are recruiting patients predominantly in CCA, almost all of them are not available in India.^[15,16] We registered a Phase 2, multicenter, multicohort, single-arm study, open-label study in India to address this orphan disease which is target rich in 65% of cases (CTRI/2020/05/025147).^[17] Patient participation and multinational representation in clinical trials are the key for rapid success in targeted enriched BTCs. The role of immunotherapy with or without chemotherapy is being studied in biliary tract cancers.^[18]

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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