Molecular profiling of biliary tract cancer: a target rich disease

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Contributions: (I) Conception and design: M Javle; (II) Administrative support: M Javle; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Biliary tract cancers (BTCs) are relatively uncommon orphan tumors that have an aggressive disease course and a poor clinical outcome. Surgery is the only curative treatment, but most patients present with advanced disease and therefore have a limited survival. Gemcitabine and cisplatin based chemotherapy has been the only widely accepted standard systemic therapy regimen in these patients but these tumors can be chemoresistant, further complicating their management. In recent times, there has been considerable research in the genetics of BTC and with the advent of new, advanced technologies like next-generation sequencing (NGS) we are achieving a greater understanding of its disease biology. With the help of NGS, we have now been able to identify actionable mutations such as in the isocitrate dehydrogenase 1 (*IDH1*), *FGFR2*, *BRAF* and *HER2/neu* genes for targeted therapeutics and correlate the genetic variations with distinct clinical prognoses. This recent genetic information has the potential to make precision medicine a part of routine clinical practice for the management of BTC patients.

Keywords: Next-generation sequencing (NGS); biliary tract cancers (BTCs); overall survival; *ARID1A*; isocitrate dehydrogenase 1 or 2 (*IDH1/2*); *FGFR2*; targeted therapy

Submitted Jul 29, 2016. Accepted for publication Aug 19, 2016.

doi: [10.21037/jgo.2016.09.01](https://doi.org/10.21037/jgo.2016.09.01)

View this article at: <http://dx.doi.org/10.21037/jgo.2016.09.01>

Introduction

Biliary tract cancer (BTC) classification

BTCs consist of tumors that arise from the epithelial cells lining the biliary tree and can be either intrahepatic cholangiocarcinoma (IHCCA), extrahepatic cholangiocarcinoma (EHCCA) or gallbladder cancer (GBC). EHCCAs are further classified as Klatskin (hilar) and distal cholangiocarcinomas (1). BTCs are heterogeneous cancers that are increasing in incidence worldwide, are often refractory to standard chemotherapy regimens and bear a poor prognosis. These cancers are associated with gallstones, inflammatory bowel disease, obesity, hepatitis, congenital cystic lesions in the bile duct or toxin exposure. The genetic alterations in BTC result in the activation of complex molecular downstream signaling pathways, altered chromatin remodeling, deregulation of DNA repair and

accelerated angiogenesis (2). BTCs are rich in actionable genetic aberrations (GA) and it is possible now to identify unique molecular subsets of BTC that can be effectively treated with an individualized approach.

Genomic landscape based on tumor location (IHCCA, EHCCA and GBC)

There has been a rising interest in the genomic landscape of BTCs with the advent of new, advanced technologies like next-generation sequencing (NGS). It has been observed that the mutational profile of BTCs vary with location of the tumor. Isocitrate dehydrogenase 1 or 2 (*IDH1/2*), *BAP1* mutations and *FGFR2* fusions are more commonly observed in IHCCA, on the other hand in EHCCA, *KRAS*, *p53* and *SMAD4* mutations are more frequent. Activating *ERBB2* and *ERBB3* mutations and inactivating *PTEN* and *TSCI*

Figure 1 The figure depicts the molecular spectrum of BTC, based on the location of the tumor. Additionally the prevalence of these mutations along with possible targeted treatment modalities has also been outlined. BTC, biliary tract cancer; IHCCA, intrahepatic cholangiocarcinoma; EHCCA, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; *IDH1/2*, isocitrate dehydrogenase 1 or 2.

mutations are seen in GBC (1,3,4). Common actionable GA, their prevalence and possible targeted treatment options based on the location of the tumor are depicted in *Figure 1*.

Genomic landscape differences seen in different patient populations (West versus East)

The etiology of the BTCs varies in different parts of the world. GBC in Asia and Latin America is associated with cholelithiasis whereas in Western Europe and North America, GBC is becoming very uncommon with the increasing use of laparoscopic cholecystectomy for symptomatic gallstones (5). In the case of cholangiocarcinoma in Southeast Asia, parasitic infection by the liver fluke, *Opisthorchis viverrini* and hepatitis B are often responsible (6,7). On the other hand in the western world, obesity, inflammatory bowel disease with sclerosing cholangitis, hepatitis C and toxin exposure have a

pathogenic role (7). It follows that there is also considerable genetic diversity between these cancers corresponding to the geographic region of occurrence.

Ong *et al.* performed whole exome sequencing of liver-fluke associated cholangiocarcinoma from Asian patients and reported mutations in *P53*, *KRAS*, *MLL3*, *ROBO2*, *RNF43*, *PEG3* and *GNAS* genes. The latter groups of genes are involved in the deactivation of histone modifiers, activation of G protein signaling and loss of genome stability (8). The same group then sequenced non-liver fluke associated cholangiocarcinoma and noted that there was a significantly higher prevalence of *P53*, *SMAD4*, *MLL3* and *GNAS* in liver fluke associated cholangiocarcinoma while non-liver fluke associated cholangiocarcinomas had a higher rate of *IDH1/2* and *BAP1* mutations (8). Similar findings were reported from an exome sequencing study from western patients with cholangiocarcinoma with a higher frequency of mutations in the chromatin modulating genes, including

ARID1A, *BAP1* and *PBRM1* being reported (9). Mutations in the *FGFR* family, including *FGFR* gene fusions/translocations have been reported in up to 10% of IHCCAs in the western patients while these mutations have not been reported to our knowledge in the liver fluke associated cholangiocarcinomas (3,10). It is evident, based on the above observations that genetic differences exist depending upon the etio-pathogenesis of cholangiocarcinoma. However, tumor location may at least partly account for these differences. Liver fluke associated cholangiocarcinoma for instance, is more likely to be extrahepatic (distal or perihilar) in location (11), which as discussed has a different genetic profile as compared with IHCCA.

Frequently dysregulated pathways

HER2/neu, HER1/EGFR signaling pathways

HER2/neu gene is a key driver of tumorigenesis in several solid tumors, including breast, non-small cell lung cancer and colorectal cancer and its overexpression as a result of gene amplification indicates an adverse prognosis. Our group recently studied *HER2/neu* protein expression in 187 cases of GBC using the accepted College of American Pathologists (CAP)/American Society of Clinical Oncology (ASCO) criteria and noted a 13% *HER2/neu* overexpression rate 3+ by immunohistochemistry (4). Yoshikawa and colleagues reported a 0.9% and 8.5% incidence of *HER2/neu* protein overexpression in intra- and EHCCA, respectively. In their series, early stage disease and well-differentiated tumors had a higher incidence of *HER2/neu* positivity (12). Data with regards to the prognostic value of *HER2/neu* overexpression in biliary cancers is mixed, with some studies suggesting a worse prognosis (13,14), while others suggest a better prognosis (12,15). Although the data regarding *HER2/neu* targeted therapy with trastuzumab in biliary cancer is limited, smaller case series indicate therapeutic benefit in GBC patients who had *HER2/neu* amplification but larger studies should be conducted to validate these findings (16). *HER2/neu* mutations in the kinase domain occur more commonly in EHCCA and maybe subjects for irreversible tyrosine kinase inhibitors (TKIs) targeting *HER2/3* and *EGFR*, such as afatinib, neratinib, and dacomitinib (3).

Abnormal activation of *EGFR* receptors, leads to activation of downstream mitogen-activated protein kinase (MAPK)/ERK and phosphatidylinositol 3-kinase (PI3K)/PTEN/AKT pathways, both of which are well-established

oncogenic pathways in BTC (17). A phase II study of erlotinib in advanced BTC indicated that *EGFR* expression was noted in 81% of cases of whom 17% experienced disease stability for 6 months (18). Lubner *et al.* further studied this signal in a multicenter phase II study of erlotinib and bevacizumab; of the 53 patients enrolled; 12% experienced partial response and stability was seen in 51% (19). A subsequent phase III study of gemcitabine, oxaliplatin ± erlotinib, showed no difference in overall survival between these two groups, however there was an improved progression-free survival and response rate in the erlotinib arm (20). These studies indicate that *EGFR* targeting in BTC continues to be an area of clinical value.

BRAF mutations occur in 5% of BTC cases, particularly in IHCCA (21-24). Impressive activity was noted in metastatic melanoma with *BRAF V600* mutations with a combination of dabrafenib (*BRAF* inhibitor) and trametinib (MEK1 and MEK2 inhibitor) (25). Loaiza-Bonilla *et al.* reported an impactful response in an IHCCA patient who received this dual therapy, using a combination of *BRAF* inhibition and a MEK inhibitor (26). This indicates the need for prospective clinical trials for BTCs patients with mutant *BRAF*.

FGFR signaling pathway

FGFR pathway GAs, particularly *FGFR* fusion genes or translocations have been described in 10–16% of IHCCA and have gained a lot of attention as potential targets for therapeutic intervention (3,27). *FGFR* fusions are very uncommon in extrahepatic or GBC and are almost exclusively seen in IHCCA only. The *FGFR* family consists of four transmembrane receptors (*FGFR* 1–4), 22 *FGFR* ligands and a heparan sulfate proteoglycan (HSPG) that stabilizes and sequesters the FGFs. The major downstream signaling routes for *FGFR* are through the Ras-Raf-MAPK, PI3K pathways and the protein-serine/threonine kinase AKT. Dysregulation of the *FGFR* pathway can occur through *FGFR* mutations, translocations, amplification, overexpression and alteration of regulatory influences such as by FGF ligand amplification. *FGFR* amplifications are rare in BTC but *FGFR2* mutations and *FGFR2* fusions occur relatively frequently in IHCCA (27). Sia *et al.* reported that *FGFR2-PPHLN1* fusions occur in up to 16% of IHCCA (28). In our experience, *FGFR2-BICC* fusion was the commonest fusion noted. Our group has investigated the prognostic role of *FGFR* pathway GAs. *FGFR2* GA, including fusion genes appears to be associated with a relatively indolent

clinical disease course of cholangiocarcinoma (29). The advent of FGFR-targeted therapies has incentivized further clinical research in this field. These therapies include multi-TKIs that also inhibit FGFR (such as ponatinib, nintedanib, dovitinib and brivanib), specific FGFR directed small molecule TKI (BGJ398, JNJ425756493, PRN1371, ARQ087, TAS-120) FGFR antibodies and FGFR trap molecules. Phase II BGJ398 results were reported recently; 50 patients with BTC having *FGFR* genetic alterations were enrolled, the majority being IHCCA. The overall response rate was 15%, disease control rate was 95% with progression-free survival of 6 months, indicating that FGFR-directed therapy is a successful investigational strategy for *FGFR* mutated cholangiocarcinoma (30).

IDH1/2 mutations in BTC

In 2008, mutations in *IDH1* and *IDH2* were first identified in glioma and acute myeloid leukemia. Subsequently, these were identified in other solid tumors including cholangiocarcinoma (31). In IHCCA, an estimated 20% have *IDH1* while 5% have *IDH2* mutations (32). These mutations are not seen in EHCCA or GBC (3,33). The most common *IDH* mutations occur in arginine residues in the catalytic pockets: *IDH1* (R132) and *IDH2* (R172 or R140) (34). *IDH1* and *IDH2* catalyzes the NADP⁺-dependent reversible conversion of isocitrate to α -ketoglutarate, whereas gain-of-function *IDH1* or 2 mutations catalyze the oxidation of α -ketoglutarate to 2 dihydroxyglutarate (2-HG), using NADPH as a cofactor (35). It is believed that 2-HG is mutagenic although the mechanism is not well understood. However, this alteration causes change in redox potential, increased CpG island and histone methylation, thus blocking cell differentiation, impaired collagen maturation and basement membrane formation. Mutant *IDH* promotes carcinogenesis by blocking hepatocyte differentiation and increasing pools of hepatic progenitors that are susceptible to additional oncogenic hits (36). *IDH1* mutation is regarded as a favorable prognostic factor in glioma. However, we and others have not found any prognostic significance to *IDH1/2* mutation in cholangiocarcinoma (32,37). Small molecule specific inhibitors against *IDH1/2* may have promising anti-tumor activity in this subgroup. Recently Burris *et al.* reported the findings of a dose-escalation study of AG-120 in various cancer types having these mutations. Of the 20 cholangiocarcinoma patients enrolled, response or stability was noted in 12 patients with the disease stability demonstrable beyond 6 months (38).

Other allosteric *IDH* inhibitors like AG-881, are currently under development for these cancers (39).

DNA repair mutations in BTC

DNA repair mechanisms are essential for maintaining genomic stability and defects in these occur in BTC. Gene mutations leading to defective DNA mismatch repair (MMR) are commonly seen in several solid tumors like colorectal cancer, endometrial and gastric cancer (40,41). Data regarding presence of MMR in BTC is limited. Goyal *et al.* reported a 9% rate of MMR protein loss in cholangiocarcinoma patients on immunohistochemistry, with 4.5% patients being microsatellite instability (MSI)-high (42). In our series of 321 BTC who underwent mutational profiling, DNA repair mutations (*MSH6*, *BRCA1*, *BRCA2*, *ATM*, *MLH1* or *MSH2* genes) occurred in 13% IHCCA, 26% in EHCCA and 6% of GBC cases (32). The subset of cancers with MMR system defects is very sensitive to programmed cell death protein 1 (PD-1) blockade using checkpoint inhibitor agents like pembrolizumab (43). Specific DNA repair inhibitors targeting homologous recombination repair, base excision repair and nucleotide excision repair are under investigation currently. BTC patients with mutations in the DNA repair pathways can represent a subset wherein targeted therapeutics in the form of specific DNA repair inhibitors or immunotherapy may be effective. Further clinical trials are needed to validate the safety and efficacy of these treatment modalities.

Mutations in chromatin remodeling genes

Inactivating genetic alterations in *ARID*, *BAP1*, *PBRM* and *MLL* that are responsible for chromatin remodeling have been noted in renal cell carcinoma uveal melanoma, ovarian, colorectal and gastric cancers. Chromatin remodeling allows genomic DNA to access regulatory transcriptional proteins and thereby controls gene expression. GA in this process have recently been implicated in the development of BTC (9). *BAP1* encodes for a nuclear deubiquitinase, while *PBRM1* and *ARID1A* both encode a subunit of the ATP dependent SWI/SNF chromatin-remodeling complexes (44,45). Jiao *et al.* observed that mutations in at least one of these genes occurred in almost half of the BTCs sequenced in their study (9). The prognostic role of mutations in chromatin remodeling genes is currently unknown, though *BAP1* mutations were associated with aggressive disease resulting in bony metastases (3). Another

case series reported 22 cases of cholangiocarcinoma with *BAP1* mutation and noted that 13 (59%) had bone metastases at presentation. These patients experienced rapid tumor progression with a mean time for tumor progression of 3.8 months (46). This study highlights the dire need to focus on *BAP1*-directed targeted therapies as currently there are no effective therapies for cholangiocarcinoma with these mutations. It is hypothesized that histone deacetylase (HDAC) inhibitors such as vorinostat and panobinostat may offer therapeutic value and need to be explored further prospectively (47).

Molecular classification with prognostic staging system/score for BTC

Cancer classification has traditionally relied upon pathologic criteria that are based on site of origin. Recent sequencing studies have highlighted that disparate cancers arising from different organ systems may harbor similar GA causing them to exhibit a clinical course and targeted therapy response that is compatible with the molecular phenotype rather than the organ of origin. For instance *BRAF* mutant cholangiocarcinoma may have clinical homology with melanoma having the *BRAF* mutation rather than with *FGFR* mutant cholangiocarcinoma. Larger genomic studies conducted with The Cancer Genome Atlas (TCGA) research in lung, colorectal, pancreas, breast, bladder, endometrial and other cancers have revealed that each of these cancers can be further subdivided into three or four more molecular subtypes based on recurrent genetic alterations that are commonly expressed. In gastric cancer, four molecular subgroups have been identified: (I) Epstein-Barr virus (EBV) type (high *PIK3CA* mutation, hypermethylation, expression of *PDL1*; (II) MSI subtype; (III) genomically stable subtype (diffuse histology, RAS mutation and genes encoding adhesion proteins); and (IV) tumors with chromosomal instability (intestinal type histology, aneuploidy and receptor TKI amplification) (48). In case of pancreatic cancer, similarly four subgroups have been proposed: (I) stable (20% aneuploidy); (II) locally rearranged (30%, focal event in one or two chromosomes); (III) scattered (36%, <200 structural variation events); and (IV) unstable (14%, >200 structural variation events, defects in DNA repair and maintenance) (49). This classification has important implications for targeted and immunotherapy. For instance, the MSI subtype and the EBV type of gastric cancers are sensitive to immune inhibition with checkpoint blockers. The 'unstable' variant of pancreatic cancer may

respond well to DNA repair blockers, such as inhibitors of poly(ADP-ribose) polymerase (PARP). TCGA analysis of cholangiocarcinoma is now complete and the expectation is that we will have a similar molecular subtyping of this disease that may result in prognostic and therapeutic stratification.

In summary, molecular analysis of BTC has been extremely instructive; this disease has considerable genetic heterogeneity that can be effectively targeted with novel agents. The plethora of actionable mutations in these orphan diseases has made precision medicine a reality.

Acknowledgements

This study was supported by Paula and Jeff Laut Foundation, Graeme and Lee Dayton Foundation. Illustrations by David Aten, MA, senior medical illustrator MD Anderson.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Jain A, Javle M. Molecular profiling of biliary tract cancer: a target rich disease. *J Gastrointest Oncol* 2016;7(5):797-803. doi: 10.21037/jgo.2016.09.01