Cholangiocarcinoma Cancer

Getting cholangiocarcinoma patients on the right treatment, faster

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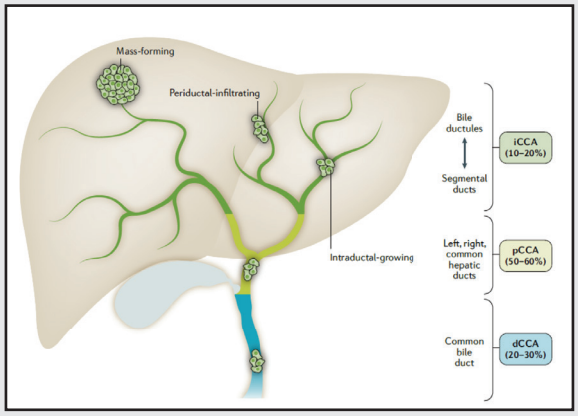
Cholangiocarcinoma is the second most common primary liver cancer in the world. It typically affects patients over the age of 65 and unfortunately has a poor prognosis. Getting these patients on the right treatment faster can make all the difference. The adoption of precision medicine can have a substantial effect on survival in patients with cholangiocarcinomal cancer!

Nat Rev Gastroenterol Hepatol

17, 557–588 (2020)

Cholangiocarcinoma 2020: the next horizon in mechanisms and management.



ESMO Open

2017 Mar 27;2(Suppl 1):e000152. doi: 10.1136/esmoopen-2016-000152.

New molecular and immunotherapeutic approaches in biliary cancer.

"Intrahepatic and extrahepatic cholangiocarciomas will have distinctly different molecular findings carrying distinctly different potential targetable treatment benefits."

Table 1 Incidence of molecular mutations in biliary tract cancer as determined by genomic sequencing

Mutation	Intrahepatic cholangiocarcinoma (%)	Extrahepatic cholangiocarcinoma (%)	Gall bladder cancer (%)
ERBB2 amplification	3	11	16
BRAF substitution	5	3	1
KRAS	15-22	42-47	11-19.2
PI3KCA substition	5	7	14
FGFR1-3 fusion	11-12.5	0	3
CDKN2A/B loss	18	17	19
IDH1/2 substitution	15-23	3-4	0
ARID1A alteration	11-20	12	11-13
MET	4	0	0
BAP1	9-25	0	4-13

CCA News AACR Highlights

August 2020, Vol 1, No 1

Early Molecular Testing Crucial for Informing Treatment Choices in Patients with Cholangiocarcinoma

"A major stumbling block to the discovery of molecular aberrations in patients with CCA (cholangiocarcinoma) has been the adoption of molecular profiling by healthcare providers. **A minority of patients with newly diagnosed CCA undergo comprehensive molecular profiling. Oncologists have been slow to incorporate these new tests effectively into routine patient care. Approximately 45% to 50% of patients with CCA have an actionable mutation and may be candidates for precise, personalized therapies alone or in combination with chemotherapy.** It is enlightening to realize that about half of patients with cholangiocarcinoma have at least one 'actionable' genomic alteration in the malignant tissue, and about 75% have a 'potentially actionable' alteration, which makes them possibly eligible for clinical studies or novel targeted treatment. I believe these data speak for the need of broader and earlier use of biomarker testing in cholangiocarcinoma patients. One of the challenges that clinicians face when trying to diagnose CCA is obtaining enough tumor tissue to conduct molecular-profiling studies. A repeated biopsy could potentially be performed, but some tumors may be difficult or dangerous to reach to obtain the necessary tissue. As an alternative, **blood testing for circulating tumor-cell DNA (ctDNA) can identify important molecular markers that could be missing** if a repeated biopsy is difficult to perform."

JCO Precis Oncology

DOI: 10.1200/PO.18.00397 JCO Precision Oncology – published online April 18, 2019

"Cancer patients may benefit from ctDNA analysis as it is a relatively easy and noninvasive way to supplement traditional diagnostics with real-time tumor information and exhibit a much greater sensitivity than other tumor biomarkers. Liquid biopsy has emerged as a minimally invasive tool to genotype tumors, to assess patient prognosis and detect MRD, to monitor treatment efficacy, and to track the dynamism of clonal evolution over time and therapies. Whereas tissue biopsies catch single snapshots of the tumor in a specific spatiotemporal fragment, liquid biopsy may more comprehensively depict the intrinsic and dynamic intratumoral heterogeneity."

CIRCULOGENE'S *comprehensive cholangiocarcinoma panel is a noninvasive technique that can be combined with traditional tissue biopsy to track cell-free DNA and detect disease biomarkers in blood faster and more accurately.*

Cholangiocarcinoma Cancer - Case Study

Real Patients, Real Results

59-YEAR-OLD FEMALE PATIENT

OBSTRUCTIVE JAUNDICE AND A PORTA-HEPATIS MASS

What is more striking than the different anatomical compartments and growth patterns of cholangiocarcinomas (CCA) is their genomic complexity and molecular diversity. ERBB2 amplification and KRAS mutations occur more frequently in extrahepatic CCA, with the targetable FGFR1-3 fusions and IDH1/2 mutations preferentially more frequent in intrahepatic CCA. A recent study utilizing a liquid biopsy next-generation sequencing (NGS) approach identified therapeutically relevant plasma ctDNA/RNA alterations in 55% of biliary tract cancers. Without broad NGS testing these targetable and actionable molecular findings would not be known. A paucity of tissue biopsy cellularity in this disease often precludes complete tissue NGS testing. However, these vital precision molecular oncology results can be obtained with liquid biopsy plasma NGS testing, ensuring patients can get the best personalized cancer treatment.

This patient's plasma NGS identifies an adverse prognostic mutation but also actionable treatment findings. The FBXW7 mutation is not directly targetable but is a very impactful, therapeutically actionable mutation. FBXW7 is a tumor suppressor gene, and when dysfunctional, is associated with epithelial to mesenchymal pathways and a very poor overall survival in CCA. It is also known to be associated with cisplatin and taxane chemotherapy resistance mediated by MCL-1 upregulation. However, fluoropyrimidine-based regimens, often with gemcitabine, have shown retained chemotherapy sensitivity and survival benefit even in FBXW7- mutated CCA. Sorafenib also has a role in FBXW7 mutation cancers by inhibiting the anti-apoptotic effect of MCL-1, achieving both therapeutic effectiveness and reversing the chemotherapy resistance. The MET E168D mutation, although not an exon14 skipping mutation, is in the extracellular domain hepatocyte growth factor (HGF) binding site leading to MET downstream activation and may result in higher sensitivity to MET inhibitors. Finally, the somatic BRCA1 mutation opens up the potential benefit of PARP inhibitors. The first step in systemic therapy, in my opinion, should be a non-platinum chemotherapy with capecitabine alone or a capecitabine/gemcitabine doublet. Second-line therapy includes strong consideration of sorafenib. A PARPi can also be effective, even in the somatic BRCA setting.

ALTERATIONS DETECTED

GENE	ALTERATION	MUTANT FRACTION	FDA TARGETED THERAPIES (lung cancer)	FDA TARGETED THERAPIES (for other indications)	CLINICAL TRIALS (DETAILS BELOW)
BRAF	No Reported Mutation		Dabrafenib not indicated	Melanoma (BRAF Wild Type): Nivolumab & Pembrolizumab Indicated; Dabrafenib, Trametinib, Vemurafenib & Cobimetinib NOT indicated	28
FBXW7	p.R473fs; c.1417delA	84.8%	None		

FBXW7 DESCRIPTION
This gene encodes a member of the F-box protein family which is characterized by an approximately 40 amino acid motif, the F-box. The F-box proteins constitute one of the four subunits of ubiquitin protein ligase complex called SCFs (SKP1-cullin-F-box), which function in phosphorylation-dependent ubiquitination. The F-box proteins are divided into 3 classes: Fbws containing WD-40 domains, Fbls containing leucine-rich repeats, and Fbxs containing either different protein-protein interaction modules or no recognizable motifs. The protein encoded by this gene was previously referred to as FBX30, and belongs to the Fbws class; in addition to an F-box, this protein contains 7 tandem WD40 repeats. This protein binds directly to cyclin E and probably targets cyclin E for ubiquitin-mediated degradation. Mutations in this gene are detected in ovarian and breast cancer cell lines, implicating the gene's potential role in the pathogenesis of human cancers. Multiple transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Mar 2012]

MET	p.E168D; c.504G>T	96.5%	None		16

MET DESCRIPTION
This gene encodes a member of the receptor tyrosine kinase family of proteins and the product of the proto-oncogene MET. The encoded preproprotein is proteolytically processed to generate alpha and beta subunits that are linked via disulfide bonds to form the mature receptor. Further processing of the beta subunit results in the formation of the M10 peptide, which has been shown to reduce lung fibrosis. Binding of its ligand, hepatocyte growth factor, induces dimerization and activation of the receptor, which plays a role in cellular survival, embryogenesis, and cellular migration and invasion. Mutations in this gene are associated with papillary renal cell carcinoma, hepatocellular carcinoma, and various head and neck cancers. Amplification and overexpression of this gene are also associated with multiple human cancers. [provided by RefSeq, May 2016]

TP53	p.P72R; c.215C>G Exon 4	100.0%	None		6

TP53 DESCRIPTION
This gene encodes a tumor suppressor protein containing transcriptional activation, DNA binding, and oligomerization domains. The encoded protein responds to diverse cellular stresses to regulate expression of target genes, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Mutations in this gene are associated with a variety of human cancers, including hereditary cancers such as Li-Fraumeni syndrome. Alternative splicing of this gene and the use of alternate promoters result in multiple transcript variants and isoforms. Additional isoforms have also been shown to result from the use of alternate translation initiation codons from identical transcript variants (PMIDs: 12032546, 20937277). [provided by RefSeq, Dec 2016]

ALTERATIONS DETECTED

GENE	ALTERATION	FDA TARGETED THERAPIES (breast/ovarian cancer)	FDA TARGETED THERAPIES (for other indications)
BRCA1	c.3329delA, p.K1110fs*7		Olaparib; Rucaparib; Talazoparib

BRCA1 DESCRIPTION
BRCA1 is a tumor suppressor involved in the DNA damage response and DNA repair (PMID: 21203981). BRCA1 germline mutations increase the risk of developing ovarian and/or breast cancer (PMID: 21285145) and somatic mutations are highest in NSCLC, pancreatic, and colon cancers (PMID: 27283171).

BRCA2	Not Detected		

BRCA2 DESCRIPTION
BRCA2 is a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair, thereby playing a role in genome stability (PMID: 27530658). BRCA2 germline mutations increase the risk of developing ovarian and/or breast cancer (PMID: 23364291) and somatic mutations are highest in coon, NSCLC, and ovarian cancers (PMID: 27283171).

Monitoring with repeat plasma NGS in 4-6 weeks will be very helpful in confirming an early molecular response with, hopefully, decreasing ctDNA mutations and comparative mutant allele fractions or the identification of resistance far earlier than standard repeat imaging, providing certainty of continuing the effective treatment or changing to another potentially effective treatment. It will also identify whether the MET mutation clone is responding to this particular regimen or persisting, reflecting clonal resistance. Any identified MET clonal persistence would warrant strong consideration for a potential MET-targeted clinical trial, given the broadening array of MET therapies developed and undergoing testing in clinical trials. Although the patient is not MSI-H, which would absolutely warrant immunotherapy, immune checkpoint inhibitors are showing sufficient promise in CCA, warranting strong therapeutic consideration. All potential therapeutic steps to target the tumor biology to help her live longer and better, can best be guided by a liquid biopsy plasma NGS.

Two additional very simple aspects of her CCA treatment and management are also quite meaningful. One is the reported overall survival benefit of simple ASA in CCA and second is the high 16% potential of CCA of having an identifiable germline mutation.

Case Study Prepared by Doctor Paul Walker
Chief Medical Officer, Former Director of Thoracic Oncology at East Carolina University

Sources:
- JAMA Oncology
- Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School,Boston, MA, USA
- ONCOLOGY LETTERS 13: 3653-3661, 201
- Nature Reviews | Clinical Oncology Reviews, volume 17 | September 2020 | 569