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Molecular characteristics of biliary tract cancer

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ABSTRACT

Biliary tract cancers (intrahepatic, perihilar and extrahepatic cholangiocarcinoma, and gallbladder and cystic duct cancers) are uncommon but highly lethal malignancies. Clinical presentation is often late, precluding curative surgical resection in most cases. For advanced disease, therapeutic options are limited to systemic chemotherapy, with suboptimal outcomes. An understanding of the molecular characteristics of biliary tract cancers may allow the clinical development of therapies targeting actionable alterations with the ultimate goal of improving clinical outcomes. We present a comprehensive review of biliary tract cancer genomics and their clinical implications. Alterations in genes in the EGFR-MAPK-PI3K pathway are seen most often. KRAS alterations are highly prevalent; BRAF alterations are mutually exclusive from RAS alterations and much less frequent. PIK3CA alterations are seen mostly in extrahepatic cholangiocarcinoma and gallbladder cancers whereas HER2 amplification is most common in gallbladder cancers. Various tumor suppressor genes, such as TP53 and p16 are also altered often in biliary tract cancers; however, agents to "activate" silenced genes are currently lacking. FGF and IDH pathway alterations are potential targets for therapeutic agents. FGF alterations are

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typically fusions with other genes, resulting in altered proteins, and are seen most often in intrahepatic cholangiocarcinoma. IDH pathway alterations affect cellular enzymatic processes and are most common in intrahepatic cholangiocarcinoma. Ongoing clinical trials of agents targeting these pathways hold the promise of improving clinical outcomes.

1. Introduction

Biliary tract cancers comprise malignancies arising from the epithelium of the biliary duct system, including the intrahepatic and extrahepatic biliary tree, the gallbladder and cystic duct. Histologically classified as adenocarcinomas, they are clinically divided into categories based on site of origin – intrahepatic, perihilar (Klatskin tumors) and extrahepatic cholangiocarcinoma, and gallbladder cancer. These tumors are relatively uncommon but continue to have a poor prognosis. Accurate statistics on biliary tract cancers are difficult to obtain because intrahepatic cholangiocarcinoma is often combined with hepatocellular carcinoma in various registries. In 2015, it is anticipated that there will be at least 11,000 cases of and 3700 deaths from biliary tract cancer in the United States alone (Siegel et al., 2015). Globally, the incidence of biliary tract cancers varies, with the highest rates seen in the Andean populations, especially Native American groups, and in women in Southeast Asia (Andia et al., 2008; Randi et al., 2006).

A clear etiologic factor is identifiable in only a minority of cases. Chronic biliary epithelial inflammation resulting from any cause is a major risk factor. Conditions leading to chronic inflammation include primary sclerosing cholangitis, liver fluke (*Clonorchis*, *Opisthorchis*) infestation, cholelithiasis or choledocholithiasis, and congenital biliary tree abnormalities such as anomalous pancreaticobiliary duct junction. The advent of genomics has led to a growing understanding of the molecular underpinnings of various malignancies. However, large series in biliary tract cancer are lacking. One reason is the lack of adequate tissue in most clinical specimens. A diagnosis is usually made on bile duct brushings or fine needle aspirates, which often yield scant tissue for molecular profiling (Sohal et al., 2015). Most studies to date are retrospective with relatively small sample sizes and disparate methods of assessing molecular alterations. A better understanding of the molecular characteristics is required to allow development and testing of targeted therapies to improve clinical outcomes. Here, we present a systematic review of current knowledge on the genomics of biliary tract cancers and describe clinical implications and future directions based on this understanding. We describe the molecular alterations seen in biliary tract cancer, and findings from clinical studies of targeted therapies acting on those alterations.

2. Methods

We conducted a comprehensive search of PubMed for all articles on the topic. The following search algorithm was used: “bile” or “biliary” or “gallbladder” or “gall-bladder”, with “neoplas-” or “cancer-” or “carcinoma-” or “adenocarcinoma-” or “tumo(u)r-” or “malignanc-”, combined with “cholangiocarcinoma-” to select relevant histology, followed by “molecular” or “genomic-” or “genetic-” or “target-” or “sequenc-” or “profil-” or “mutation-” or “alteration-” to select articles pertaining to the study topic. Limiting to English language, there were 481 articles. Non-human studies were removed. Bibliographies of remaining articles, including previous reviews, were checked for cross-referencing. Some studies were updates of prior publications, with additional samples, and these were noted.

All articles were reviewed and relevant data were extracted into a simple dataset containing article and study characteristics, number of patients and specimens in each study, exact location and histology of tumors, genes profiled, method of molecular assaying, and results. The focus was on results with clinical implications, such as description of genomic alterations in biliary tract cancers, their prognostic and predictive role, and potential value as therapeutic targets. Previously published clinical reviews, abstracts of studies present at major scientific meetings, and publicly available databases of ongoing clinical trials in biliary tract cancers were also searched to gather data on current and future directions in the field (Fig. 1).

3. Current technologies

There has been remarkable progress in the methods to assess molecular characteristics of tumors (MacConaill, 2013). Current methods include span from hotspot sequencing of single genes to whole genome and whole exome sequencing (Damodaran et al., 2015). For most clinical situations, targeted gene assays are used. These assays are based on a massively parallel (or next-generation) sequencing platform and the panels comprise anywhere from a few to a few hundred genes. Some are commercially available, and others are housed in pathology and research laboratories. For clinical purposes, a CLIA (Clinical Laboratory Improvement Amendments, 1998) certification of the assay is highly preferred. Users should familiarize themselves with operating characteristics of the assay – whether hotspots or entire sequences are evaluated, whether fresh or archived tissue is required, whether large alterations (beyond the usual 200–2000 base pair splices) and fusions are evaluated or not, sample amount (tumor content) and purity (tumor proportion) requirements, and sensitivity, specificity and algorithmic cutoffs (for calling alterations, amplifications, deletions). These characteristics can vary widely among different assays (Van Allen et al., 2013). Usually, 20-80 μm of tissue (which is roughly 10–15 slides, depending on thickness and tumor content) is required for most platforms, and turnaround times are usually 2–4 weeks.

For biliary tract cancers, tissue specimens are difficult to obtain, however. Most patients present with advanced disease, where surgery is not applicable. In the absence of a surgical specimen, tissue sequencing can be difficult because most clinical diagnostic specimens are obtained via bile duct brushings, either endoscopic or percutaneous (for gallbladder and extrahepatic tumors), or percutaneous liver lesion aspirates (for intrahepatic tumors). For most sequencing platforms, however, these samples do not contain enough tissue to allow genomic assays (Sohal et al., 2015). Therefore, an effort should be made to obtain larger tissue samples through core biopsies. Current endoscopic methods are expanding to allow such core biopsies (Inoue et al., 2016).

Timing of sequencing is context-dependent. However, given paucity of good therapies (beyond gemcitabine-platinum chemotherapy combinations) for biliary tract cancer, it is reasonable to obtain tumor sequencing in the early phases of front-line therapy. This can allow identification of potential therapeutic targets early, helping decisions on subsequent lines of therapy as well as appropriate clinical trial enrollment.