Roles of Novel Biologics in Biliary Cancers

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Biliary tract cancers represent a diverse group of epithelial malignancies arising from the biliary epithelium including the gallbladder, intrahepatic and extrahepatic bile ducts. These anatomic subtypes differ both in terms of biology and prognosis; more recently it has become clear that they also have differing molecular profiles, with varying driver genetic aberrations according to differing anatomic locations. Both the incidence of and mortality from cholangiocarcinoma in the United States are increasing, which may be due in part to increased recognition of the diagnosis of biliary cancer. The majority of cases present with advanced disease, and systemic chemotherapy is standard of care for management of advanced biliary cancer (ABC). Initial studies evaluating single-agent 5-FU-based chemotherapy demonstrated a response rate of approximately 10%. Subsequently, gemcitabine became the most widely used drug in biliary tract malignancies, primarily as a result of its established primacy for treatment of pancreas cancer. More recently, the activity of gemcitabine and cisplatin was confirmed in the ABC-02 trial, a randomized phase III trial comparing the combination with gemcitabine alone in patients with advanced (unresectable, recurrent or metastatic) biliary tract cancers. This was a randomized trial which enrolled approx 200 patients in each arm; gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 were given weekly for two weeks followed by a week of rest for a total of four cycles. Compared to gemcitabine, combination therapy improved overall survival (11.7 vs 8.1 months, p<0.001), progression-free survival (8.0 vs. 5.0 months, p<0.001) and disease control (81.4% vs. 71.8%, p = 0.049). Differential activity was not seen among the various sites along the biliary tree.

There is no standard of care for second line treatment of ABC, the median PFS with 2nd line chemotherapy is approximately 60-90 days indicating the relatively chemo refractory nature of ABC following progression on 1st line combination chemotherapy. Molecular profiling of biliary cancers with whole exome and transcriptome sequencing has revealed several potential targets for intervention. Intrahepatic cholangiocarcinoma harbors relatively common genetic alterations in metabolic enzymes (IDH1/2), tyrosine kinase signaling molecules (EGFR, BRAF), and chromatin remodeling genes (ARID1A, BAP1), along with tyrosine kinase fusion proteins (FGFR2, ROS1). Gallbladder cancers may contain driver mutations in ERBB3, PTEN, MLL2/3; while mutations in ELF3 and PRKACA fusions have been identified in extrahepatic cholangiocarcinomas. Several ongoing clinical trials are selecting patients based on molecular criteria, evaluating targeted therapies including pan FGFR inhibitors, IDH1/2 inhibitors. Future trials in advanced BTM may consider patient selection based on anatomic location and/or molecular subtype.