



Mini Review

Advances in Cholangiocarcinoma Treatment in the Personalized Medicine Era

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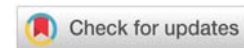
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Cholangiocarcinoma is amongst the most common primary tumors of the liver, second only to hepatocellular carcinoma, and it accounts for approximately 15% of primary hepatic malignancies [1]. Cholangiocarcinoma is sub-classified as intrahepatic (ICCA), perihilar (PCCA) or distal (DCCA), according to its anatomical location [2]. Regardless of location, cholangiocarcinoma carries a poor prognosis, mainly due to paucity of effective therapy options and advanced disease at presentation. The American Cancer Society determined a 5-year relative survival rate of 8% for all patients with intrahepatic bile duct cancer and 10% for its extrahepatic counterpart. Even localized disease carries poor survival of 24% and 15% for ICCA and extrahepatic cholangiocarcinoma, respectively [3].

While surgical resection remains the only curative option, other treatments options for non resectable cholangiocarcinoma remain scarce. Advances in systemic adjuvant therapy have seen recently reported as in the BILCAP study [4]. No definite standard of care had been established until 2010 when the combination of cisplatin and gemtacin was proven to be effective in patients with locally advanced and metastatic disease. median Overall Survival (mOS) of 11.7 months was achieved with combination therapy compared to 8.1 months achieved with gemcitabine monotherapy [5]. Little advancement has been made in the treatment of cholangiocarcinoma since 2010. The next breakthrough occurred with the introduction of Next Generation Sequencing (NGS) into clinical practice over the recent years. NGS allowed for effective extraction of tumor genomic information, leading to a new criteria to define cancer and its genomic composition, thereby aiding

the delivery of personalized medicine with targeted therapies directed towards driver mutations [6].

NGS utilization in cholangiocarcinoma

NGS analyses in cholangiocarcinoma revealed myriad of genetic mutations, with notable actionable driver mutations identified, leading to the development of targeted therapy. *Gagan et al.* led a retrospective study looking at NGS results in 195 patients with intrahepatic and extrahepatic cholangiocarcinoma [6]. In patients with ICCA, commonly seen mutations were, IDH1 (30%), ARID1A (23%), BAP1 (20%), TP53 (20%) and FGFR2 fusion (14%) [6], while patients with extrahepatic cholangiocarcinoma were more likely to have KRAS, SMAD4 and STK11 mutations [7]. Similarly, *Goyal, et al.* performed NGS analysis on ctDNA extracted through plasma samples taken from 751 patients with cholangiocarcinoma. Commonly detected mutations were TP53 (39%), KRAS (15%), PIK3CA (13%), ARID1A (13%), EGFR (11%), FGFR2 (11%), ERBB2 (11%), NF1 (10%), IDH1 (10%), APC (9%), BRAF (9%), MYC (8%), MET (7%), CCNE1 (7%), and FGFR1 (7%) [7]. One important observation from these studies is the presence of various mutations within the same tumor/patient, with an average of 3 mutations per sample which could potentially translate to multiple objectives for the development of targeted therapies [7,8].

The identifications of genetic alterations in patients with cancer has led the development of multiple new pharmacological agents, however, until recently no advancement had been



seen in cholangiocarcinoma treatment. In April 2020, the FDA approved Pemigatinib an FGFR inhibitor for the treatment of patients with either previously treated, unresectable, locally advance or metastatic cholangiocarcinoma with a FGFR2 fusion [9]. In a phase 2 trial [10], Pemigatinib had an overall response rate of 14.8%, a disease control rate of 75.4% and progression free survival of 5.8 months for all patients with advance or metastatic cholangiocarcinoma with FGFR2 fusion or other alteration, who progressed while on gemcitabine-based therapy. As mentioned, IDH1 mutations have been observed in 10%-30% of cholangiocarcinomas [7,8]. Ivosidenib, an oral IDH1 inhibitor, has been approved for the treatment of acute myeloid leukemia, and its effectiveness in patients with solid tumors is currently under investigation [11]. More recently, in the phase III ClarIDHy study, ivosidenib was proven to be effective in the treatment of previously treated advanced IDH1 mutated intrahepatic cholangiocarcinoma, with a Progression Free Survival (PFS) of 2.7 months (PFS in placebo group of 1.4 months) [11]. Aguado, et al. [12] were also successful at detecting this mutation on plasma extracted ctDNA and NGS analysis, with a high concordant rate to tissue NGS. This study demonstrated that genomic information about cholangiocarcinoma could be effectively and accurately achieved via noninvasive modality of liquid biopsy and serve as an alternative when tissue sampling is not performed or was contraindicated.

Understanding the genetic composition of cholangiocarcinoma can potentially identify disease subsets with distinct prognostic and therapeutic implications. This does not only aid with direction of therapy and the development of novel targeted therapies, but also provides important information about prognosis and predicts disease course that would guide shared decision making. Churi, et al. [13] were able to associate different mutations along with the prognostic and therapeutic implications of findings. In their study, patients with intrahepatic cholangiocarcinoma with KRAS, TP53 and MAPK/mTOR mutations had a worse outcome, compared to FGFR genetic aberration which were associated with a more indolent course.

TMB high and checkpoint inhibitors

Tumor mutational burden (TMB) is a genomic biomarker that measures the number of mutations within a tumor genome and has already been shown to be associated with improved responses to checkpoint inhibitor anti-Programmed Death-1 (anti-PD-1) in several solid tumors [14]. Several studies have demonstrated effectiveness of anti-PD-1 antibody therapy in patients with chemotherapy-resistant cholangiocarcinoma and high tissue TMB, regardless of PD-L1 positivity [15,16]. Recent studies in patients with metastatic castrate resistance prostate cancer, has shown that plasma ctDNA analysis might be suitable for the quantification of TMB [17].

In summary, cholangiocarcinoma has been historically associated with a very poor prognosis, mainly due to the scarcity of effective therapeutic options for patients with a non resectable disease. For years, gemcitabine based therapy was considered the goal standard as the treatment of intrahepatic cholangiocarcinoma. Recent FDA approval of pemigatinib for patients with previously treated, unresectable, locally advance

or metastatic cholangiocarcinoma - has changed the treatment paradigm in cholangiocarcinoma. By targeting the FGFR2 fusions or rearrangements, pemigatinib provided additional benefits to patients who have exhausted previous lines of treatment, and allowed for the delivery precision medicine. This advancement was made possible as a direct result of the increasing utilization of genomic analysis, via NGS and others techniques, leading to the development of targeted therapies options for patients with advanced or relapsed cholangiocarcinoma. Current research directed towards the utilization of isocitrate dehydrogenase-1 (IDH1) inhibitor, ivosidenib, in cholangiocarcinoma patients with commonly mutated IDH1 gene, and would potentially add further targeted therapeutic options for those patients. Furthermore, the possibility of combining targeted therapies was presented in the ROAR trial¹⁸. In this phase II trial reported *Subbiah et al.*, the combination of dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, achieved a substantial overall response rate in patients with BRAF V600E mutated cholangiocarcinoma.

Further research is needed to identify different driver mutations that would act as potential targets for directed therapeutic options.

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