ISSN: 2755-0176

Journal of Cancer Research Reviews & Reports

SCIENTIFIC Research and Community

Short Communication

Open Access

Advances in Cholangiocarcinoma Treatment in the Personalized Medicine Era

Kathrin Dvir[1], Gliceida M. Galarza Fortuna[1]*, Veronica Guerra[1], Nathaly Cortez[1], Mike Cusnir[2]

[1]Department of Internal Medicine, Mount Sinai Medical Center, Miami Beach, FL 33140, USA

[2]Mount Sinai Comprehensive Cancer Center, Miami Beach, FL 33140, USA

***Corresponding author**

Gliceida Galarza, MD, Mount Sinai Medical Center of Florida, 4300 Alton, Road, Miami Beach, FL 33140, USA; Tel: (786) 495-7761; E-mail: gliceida.galarza@gmail.com

Received: November 24, 2020; **Accepted:** November 27, 2020; **Published:** December 02, 2020

Cholangiocarcinoma is among the liver's most common primary tumors, second only to hepatocellular carcinoma, and it accounts for approximately 15% of primary hepatic malignancies. Cholangiocarcinomas are sub-classified into intrahepatic (ICCA) and extrahepatic (ECCA), according to their anatomical location. Regardless of their location, cholangiocarcinomas are associated with a poor outcome, mainly because of the lack of effective therapy options and how advanced the disease is at the time of diagnosis, making it difficult to control with surgical resection. 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, with the best survival rate seen on patients with localized disease, 24% for ICCA and 15% for ECCA [1-3].

Treatment options for cholangiocarcinoma that is not curative with surgical resection have remained scarce. No definite standard of care had been established until 2010 when the combination of cisplatin and gemcitabine was proven to be effective for patients with locally advanced and metastatic disease; with a median overall survival (mOS) of 11.7 months compared to the 8.1 months achieved with gemcitabine monotherapy; regimen adopted from its use with pancreatic cancer [4]. Since then, little advancement has been made in the treatment of cholangiocarcinoma.

The introduction of Next Generation Sequencing (NGS) has allowed for a way of collecting genomic information about cancer, leading to new criteria to define cancer – its genetic mutations – and aiding the development of personalized medicine with targeted therapy upon the results of DNA sequencing [5].

What Does This Mean in the Treatment of Cholangiocarcinoma?

NGS analysis in cholangiocarcinoma has revealed that this is a heterogeneous condition with a myriad of genetic mutations, some of which could be actionable, leading to the development of targeted therapy. Lowery et al. lead a retrospective study of tissue samples for NGS in 195 patients diagnosed with cholangiocarcinoma, 78% intrahepatic, and 22% extrahepatic. In patients with ICCA, the most commonly seen altered genes were IDH1 (30%), ARID1A (23%), BAP1 (20%), TP53 (20%), and FGFR2 fusion (14%). On the other hand, patients with extrahepatic cholangiocarcinoma were more likely to have KRAS, SMAD4, and STK11 mutations. Similarly, Goyal et al. collected plasma of 751 patients with cholangiocarcinoma for ctDNA analysis using Guardant360 liquid biopsy assay. The most commonly seen mutations in their cohorts 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%). One important observation from these studies is the presence of various mutations within the same tumor/patient, intra-tumor heterogeneity, with an average of 3 mutations per sample, which could potentially translate to multiple objectives for the development of targeted therapy [6,7].

Identifying genetic alterations in patients with cancer has led to the development of multiple new pharmacological agents; however, no advancement had been seen in cholangiocarcinoma treatment until recently. For instance, specific biomarkers such as microsatellite instability (MSI) - high and defects in DNA mismatch repair (MMR) had a significant clinical role in developing immune checkpoint blockade drugs such as Pembrolizumab, an anti-PD-1 antibody. In 2017 the FDA approved the use of pembrolizumab for unresectable or metastatic MSI-high or MMR-deficient solid tumors that failed previous therapies, including cholangiocarcinoma. In April 2020, the FDA approved Pemigatinib, an FGFR inhibitor for treating patients with either previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma with an FGFR2 fusion. In a phase 2 trial, 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 advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other alteration in patients who had progressed while on gemcitabine-based therapy [8-10].

As mentioned above, IDH1 mutations have been observed in 10%-30% of cholangiocarcinoma [6,7]. Ivosidenib, a mutant IDH1 inhibitor with an oral formulation, has been approved to treat acute myeloid leukemia, and its possible use in patients with solid tumors is currently under investigation. More recently, in the phase III ClarIDHy study, Ivosidenib was proven to effectively treat previously treated advanced IDH1 mutated intrahepatic cholangiocarcinoma showing a progression-free survival (PFS) of 2.7 months (PFS in the placebo group of 1.4 months). Aguado et

al. successfully detected IDH1 mutation on the plasma of affected patients by circulating tumor DNA (ctDNA) analysis with a high concordance rate to tissue NGS, allowing liquid biopsy to be a feasible and minimally invasive tool for the genetic classification of patients with cholangiocarcinoma [11,12].

Understanding the genetic classification of cholangiocarcinoma does not only lead to the direction of therapy and development of novel target therapy, but it also provides the clinician with important information with regards to the prognosis of the disease that needs to be used to educate the patient to allow for shared and informed decision making. Utilizing NGS, Churi et al. were able to associate different mutations with prognosis in patients with cholangiocarcinoma. In their study, patients with intrahepatic cholangiocarcinoma with KRAS, TP53, and MAPK/mTOR mutations had a worse prognosis compared to FGFR genetic aberration, which is associated with a more indolent course [13].

Lastly, tumor mutational burden (TMB) has recently been associated with the predicted response to anti-Programmed Death-1 (anti-PD-1) response; this relationship was initially hypothesized given the positive response to anti-PD-1 therapy in patients with colorectal cancer with mismatch repair deficiency, which is linked to a high TMB; when compared to those with mismatch repair proficient and a lower TMB burden. Several case studies have shown promised utility of anti–PD-1 antibody therapy in patients with chemotherapy-resistant cholangiocarcinoma with a high tissue TMB regardless of PD-L1 positivity. Recent studies in patients with metastatic castrate-resistant prostate cancer, has shown that plasma ctDNA analysis might be suitable for the quantification of TMB [14-17].

Historically, cholangiocarcinoma has been associated with an abysmal prognosis with minimal therapy options when the disease is not amenable by surgical resection. For years, gemcitabine-based therapy has remained the gold standard for the treatment of intrahepatic cholangiocarcinoma. More recently, NGS has opened the door of genetic profiling cholangiocarcinoma leading to the development of new therapeutic options for this dreaded disease. To date, pemigatinib is the only FDA approved directed therapy option for patients with previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma in the presence of an FGFR2 fusion. However, research is currently undergoing for the utilization of ivosidenib, and isocitrate dehydrogenase-1 (IDH1) inhibitor, in cholangiocarcinoma patients with mutated IDH1 and would potentially add further targeted therapeutic options for those patients.

Furthermore, the possibility of combining targeted therapies was presented in the ROAR trial [18]. 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. The introduction of tumor GNS and plasma ctDNA analysis has widened the knowledge of cholangiocarcinoma genetic make-up, which is currently translating into new and exciting therapeutic options.

References

1. Macias RIR, Banales JM, Sangro B, Jordi Muntané, Matias A Avila, et al. (2018) The search for novel diagnostic and prognostic biomarkers in cholangiocarcinoma. Biochim Biophys Acta - Mol Basis Dis 1864: 1468-1477.
2. Rizvi S, Khan SA, Hallemeier CL, Robin K Kelley, Gregory J Gores, et al. (2018) Cholangiocarcinoma-evolving concepts and therapeutic strategies. Nat Rev Clin Oncol 15: 95-111.
3. The American Cancer Society medical and editorial content team. Survival Rates for Bile Duct Cancer, https://www.cancer.org/cancer/bile-duct-cancer/detection-diagnosis-staging/survival-by-stage.html#written_by (2020).
4. Weigt J, Malfertheiner P (2010) Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. Expert Rev Gastroenterol Hepatol 4: 395-397.
5. Gagan J, Van Allen EM (2015) Next-generation sequencing to guide cancer therapy. Genome Med 7: 1-10.
6. Lowery MA, Ptashkin R, Jordan E, Michael F Berger, Ahmet Zehir, et al. (2018) Comprehensive Molecular Profiling of Intrahepatic and Extrahepatic Cholangiocarcinomas: Potential Targets for Intervention. Clin Cancer Res 24: 4154-4161.
7. Goyal L, Kate Kelley R, Kiedrowski L (2018) Abstract A183: Blood-based genomic profiling of cell-free tumor DNA (ctDNA) in patients with biliary tract cancer. A183-A183.
8. Pellino A, Loupakis F, Cadamuro M, Vincenzo Dadduzio, Matteo Fassan, et al. (2018) Precision medicine in cholangiocarcinoma. Transl Gastroenterol Hepatol 3: 40-40.
9. Hoy SM (2020) Pemigatinib: First Approval. Drugs 80: 923-929.
10. Javle M, Lowery M, Shroff RT, Karl Heinz Weiss, Christoph Springfeld, et al. (2018) Phase II study of BGJ398 in patients with FGFR-Altered advanced cholangiocarcinoma. J Clin Oncol 36: 276-282.
11. Lowery MA, Burris HA, Janku F, Rachna T Shroff, James M Cleary, et al. (2019) Safety and activity of ivosidenib in patients with IDH1-mutant advanced cholangiocarcinoma: a phase 1 study. Lancet Gastroenterol Hepatol 4: 711-720.
12. Aguado E, Abou-Alfa GK, Zhu AX, Teresa Macarulla, Bin Fan, et al. (2020) IDH1 mutation detection in plasma circulating tumor DNA (ctDNA) and association with clinical response in patients with advanced intrahepatic cholangiocarcinoma (IHC) from the phase III ClarIDHy study. J Clin Oncol 38: 4576-4576.
13. Churi CR, Shroff R, Wang Y, Asif Rashid, HyunSeon C Kang, et al. (2014) Mutation Profiling in Cholangiocarcinoma: Prognostic and Therapeutic Implications. PLoS One 9: e115383.
14. Yarchoan M, Hopkins A, Jaffee EM (2017) Tumor Mutational Burden and Response Rate to PD-1 Inhibition. N Engl J Med 377: 2500-2501.
15. Gbolahan O, Hashemi-Sadraei N, O'Neil B (2019) Prolonged response to Anti-PD-1 antibody therapy in chemotherapy-refractory cholangiocarcinoma with high tumor mutational burden. JNCCN J Natl Compr Cancer Netw 17: 644-648.
16. Mou H, Yu L, Liao Q, Xuehua Hou, Yinfang Wu, et al. (2018) Successful response to the combination of immunotherapy and chemotherapy in cholangiocarcinoma with high tumour mutational burden and PD-L1 expression: A case report. BMC Cancer 18: 1-5.
17. Qiu P, Poehlein CH, Marton MJ, Omar F Laterza, Diane Levitan, et al. (2019) Measuring Tumor Mutational Burden (TMB) in plasma from mCRPC Patients Using Two Commercial NGS Assays. Sci Rep 9: 2018-2020.
18. Wainberg ZA, Lassen UN, Elez E, Antoine Italiano, Giuseppe Curigliano, et al. (2019) Efficacy and safety of dabrafenib and trametinib in patients with BRAF V600E–mutated biliary tract cancer: a cohort of the ROAR basket trial. ASCO GI. J Clin Oncol 37: 187.