The clinical consequences of molecular heterogeneity of CCA and the prospect of a precision based medical treatments

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Introduction

Biliary tract cancers, including cholangiocarcinoma (CCA), are rare and represent 3% of all gastrointestinal malignancies in adults. CCA are a heterogeneous group of malignancies with different clinical and molecular characteristics [1]. Looking at their location, they are divided in intrahepatic cholangiocarcinoma (iCCA) and extrahepatic cholangiocarcinoma (eCCA) [eCCA are further divided in hilar cholangiocarcinoma (hCCA) and distal cholangiocarcinoma (dCCA)] [2].

There is an urgent need to improve outcomes for patients diagnosed with biliary tract malignancies [3]. In addition to the development of strategies for early-detection and novel biomarkers, development of novel therapeutic approaches are urgently needed, since majority of patients are still diagnosed with advanced stages when palliative treatment is the only option of management [2, 4-6]. One of the tools for development of new treatment strategies is the better understanding of the molecular heterogeneity within CCA and the development of drugs to target these findings; so called, Precision Medicine [7].

Current clinical scenario

In the palliative setting, standard of care first-line treatment remains to be cisplatin and gemcitabine chemotherapy. This is based on the ABC-02 clinical trial data [8]. Alternative palliative chemotherapy approaches, mainly in the form of new drugs (i.e. NUC-1031) [9] or triplet combinations (i.e. with the addition of nab-paclitaxel) are being developed [10]. After progression to cisplatin and gemcitabine, FOLFOX (5-fluorouracil and oxaliplatin) chemotherapy has shown an improvement in overall survival over active symptom control alone and seems to be the preferred second-line chemotherapy choice [11].

The above treatment pathway is being drastically changed by the development of targeted therapies, which have provided new and effective treatment options for patients diagnosed with tumours harbouring specific molecular alterations [7]. These approaches are currently under development and are likely to become standard of care in the coming years [3].

Molecular heterogeneity in CCA

Available data suggests that there is a marked molecular heterogeneity with the different CCA subtypes (Figure 1), with a predominance of fibroblast growth factor receptor (FGFR)-2 fusions and isocitrate dehydrogenase (IDH)-1 mutations in iCCA, while alterations in HER pathway are of more prevalence in eCCA [7] [12]. Other potential targeted therapies have been described across a small proportion of CCA patients, with no significant preference for a CCA subgroup: chromatin remodeling genes (ARID1, BAP1 and PBRM1), BRAF and RNF43 mutations, or NTRK fusions [7]. Overall, it is estimated that targetable findings are identified in around 40% of iCCA (lower proportion of eCCA) [12].

Implications of molecular heterogeneity: targeted therapies in CCA

Isocitrate Dehydrogenase (IDH) as a therapeutic target

Around 10-20% of iCCA are expected to harbour a mutation in IDH-1. AG-120 (Ivosidenib, Agios®) is one of the IDH inhibitors in more advanced stages of development in CCA. When tested in a phase I clinical trial including 73 patients with advanced mutant-IDH-1 CCA [12], ivosidenib was found to be safe and reported to achieve partial response in of 5% of patients with median PFS of 3.8 months (95% CI 3.6-7.3). Following these results, the ClarIDHy phase III clinical trial explored ivosidenib over placebo in IDH-1 mutant (R132C/L/G/H/S mutation variants) CCA after progression to prior chemotherapy [13], following a 2:1 randomisation design. The study met its primary end-point and showed a benefit in terms of PFS (HR 0.37 (95% CI 0.25-0.54; p-value <0.001)) with median PFS of 2.7 months and 1.4 months for ivosidenib and placebo, respectively.

The role of Fibroblast Growth Factor Receptor (FGFR)

Alterations in FGFR identified in CCA are mainly located in the gene encoding for FGFR2, with around 15-20% of iCCA presenting a FGFR2 fusion [14]. Despite BICC1 being one of the most frequent fusion companions for FGFR2, multiple other partners have been identified [7]. Multiple selective inhibitors of the tyrosine kinase domain of FGFR2 are under development, most of which have shown adequate safety in phase I trials and efficacy in phase II studies in patients with refractory iCCA [7]. Studies have reported a consistently high partial response rate (varying between 20.7% and 35.5%) for heavily-pretreated patients with iCCA harbouring FGFR2 fusion with median PFS around 6 months [7]. Currently, some of these agents are moving into phase III clinical trials exploring their potential role in the first-line setting compared to cisplatin and gemcitabine chemotherapy [Pemigatinib-INCB054828 (FIGHT-302; NCT03656536), Infigratinib-BGJ398 (PROOF; NCT03773302)] and focused on patients with FGFR2 fusions.

Conclusion

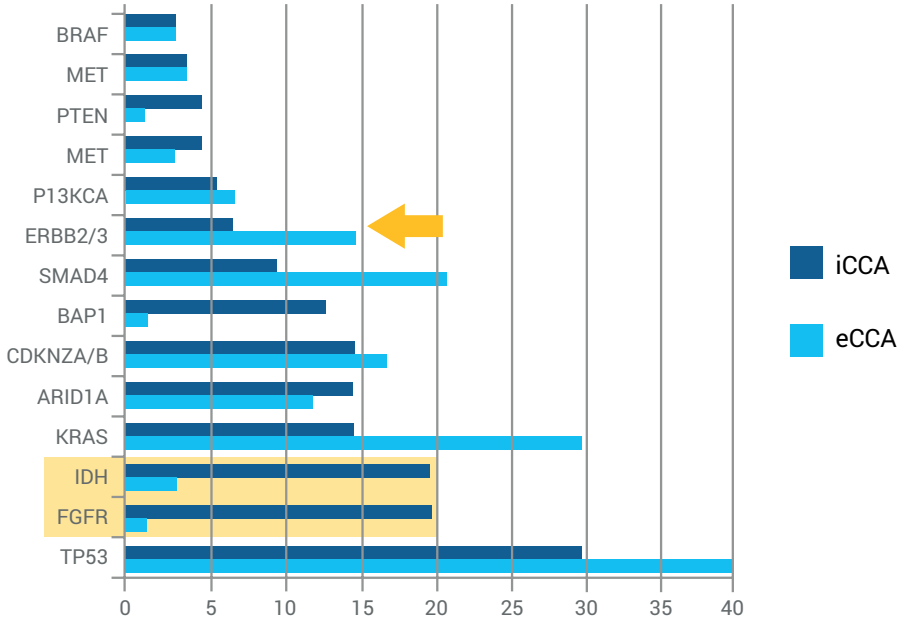
Despite recent advances and promising steps in the field, there are some challenges being faced that need to be addressed. First, is the fact that the above-mentioned targetable findings are not present in all patients; therefore, identification of new targets is crucial to allow a higher proportion of patients to benefit for Precision Medicine strategies. Second, and mainly related to the tumour location, it is expected that even in the presence of a biopsy sample sufficient for diagnostic purposes, around 25% of samples will fail molecular profiling analysis, thus highlighting the importance of innovative approaches, such as circulation tumour DNA (ctDNA) analysis for such purpose [15].

Further steps for the development of these treatments would require defining their appropriate sequencing with available chemotherapy, and to better understand the primary and secondary mechanism resistance mechanism [7]. The field is moving forward quickly, and existing years are to come.

Figure

Figure 1: Molecular heterogeneity of CCA

Yellow box and arrow highlight the main targetable alterations of interest (Adapted from 1, 7, 14, 15)



Conflict of interest

Angela Lamarca: Travel and educational support from Ipsen, Pfizer, Bayer, AAA, SirtEx, Novartis, Mylan and Delcath. Speaker honoraria from Merck, Pfizer, Ipsen and Incyte. Advisory honoraria from EISAI, Nutricia Ipsen, QED and Roche. Member of the Knowledge Network and NETConnect Initiatives funded by Ipsen.

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