

# Cholangiocarcinoma in the Era of Precision Medicine

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Cholangiocarcinoma (CCA) encompasses a spectrum of heterogeneous malignancies of the biliary tree within (iCCA) and outside (eCCA) the liver with poor prognosis. For most patients, treatment options are limited to palliative chemotherapy, because of the late diagnosis that precludes surgery, currently representing the cornerstone of cure. Notwithstanding, the treatment paradigm for CCA is rapidly evolving, due to the employment of cutting-edge technologies such as next-generation sequencing (NGS). The use of NGS has led to an unprecedented understanding of CCA tumor biology, unravelling the complex and heterogeneous genomic landscape of this disease and identifying a repertoire of actionable alterations in over 40% of patients [1]. Currently, precision medicine in CCA treatment remains confined to iCCA patients positive for isocitrate dehydrogenase 1 (IDH1) mutations and fibroblast growth factor receptor 2 (FGFR2) fusions, for which the oral FGFR inhibitors Pemigatinib and Infigratinib and the oral mutant IDH1 inhibitor Ivoselinib have been recently approved [2]. However, this cohort of patients represents a relatively small population of CCAs and for most patients, effective targeted therapies are still lacking. Accordingly, other potential actionable targets are under investigation and include ARID1, BAP1, and PBRM1 chromatin remodelling genes, BRAF and RNF43 mutations, HER2 amplifications, NTRK fusions and DNA damage repair (DDR) aberrations [3]. In addition, immunotherapy is also utilized for identification of its therapeutic niche in CCA treatment. To date, apart from a very small subgroup of patients with microsatellite instability, most of CCA patients receiving immunotherapy as single treatment experienced minimal clinical benefit. Promising results have come in the advanced setting where, compared to chemotherapy alone, the addition of durvalumab to first-line treatment significantly improved overall survival and progression-free survival in these patients [4].

Despite these efforts, the development of precision medicine in CCA remains a challenge. Indeed, although the therapeutic relevance of molecular profiling in CCA patients has been recently highlighted by the European Society for Medical

Oncology (ESMO) guidelines, which recommend the use of multigene NGS panels covering level I alterations as a routine clinical practice in advanced disease [5], currently most of CCA patients get access to tumor molecular profiling only by enrolment in a clinical trial. Moreover, most of these trials are focused only on iCCA, thus hampering the identification of novel targets and the development of new drugs for patients with extrahepatic and hilar CCAs.

Another important issue making the development of precision medicine challenging in CCA is the recovery of an adequate tissue sample for sequencing analyses by tumor biopsy, as this procedure is often technically difficult to perform in these patients, especially in extrahepatic and hilar CCAs. Moreover, single tumor biopsy may lead to an underestimated or biased identification of the mutational landscape in these tumors, which are often characterized by multi-focal lesions at the primary site even at diagnosis. This would necessitate repeated biopsies, thus exposing these patients to the well-known risks associated with this procedure. In this scenario, genotyping of circulating tumor (ct)DNA (the so-called “liquid biopsy”) may represent a less invasive and more promising strategy for monitoring tumor genomic evolution and for identifying actionable genomic alterations in real time during therapy [6]. Unfortunately, despite previous studies having reported a concordance of 74% between ctDNA and tissue DNA in CCA patients (reaching 92% for iCCA) [7], this approach is rarely applied in CCA management, even in those patients for which tumor biopsy is unfeasible.

In summary, treatment paradigm of CCA is expected to change in the next few years. In the current era of precision medicine, only a small and very specific subpopulation of CCA patients have access to precision medicine approaches in clinical practice. In this scenario, a better understanding of the genetic make-up driving CCA carcinogenesis is mandatory to identify additional actionable targets that can guide treatment decisions and improve the clinical outcome of these patients. Progress in the management of CCA will require a close collaboration between basic science and clinical research, in order to provide more effective measures that might modify the course of this aggressive and dismal malignancy for the better.

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