The promise of precision medicine: how biomarkers are shaping the future of cholangiocarcinoma treatment

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Cholangiocarcinoma (CCA) is the second most frequent primary malignant neoplasm of the hepatobiliary system. Unfortunately, CCA is often diagnosed at an advanced stage, when potentially curative surgical treatments are not recommended. The probability of achieving complete resection in patients who undergo surgery is about 25% (1) and even when complete tumor removal is achieved, the risk of recurrence is greater than 50%. Identification and validation of reliable biomarkers is crucial for the early detection, accurate diagnosis, appropriate staging/prognosis, therapy selection and effective monitoring of patients with biliary tract cancers (BTCs) (*Figure 1*). Achieving early diagnosis remains a challenge to improve survival and, although many promising biomarkers have been identified (2), to date none have reached clinical practice.

As pointed out by Munugala *et al.* (3) conventional chemotherapy regimens offer limited survival benefit for patients with advanced CCA, as some do not respond, and others progress after an initial response, being the 5-year survival of only 5–10% (4). In fact, these tumors are

characterized by limited response to chemotherapy (5) and, at present, no biomarkers are available to predict which patients will respond to chemotherapy, despite numerous studies have attempted to identify predictive biomarkers (2). The phase III SWOG 1815 trial did not demonstrate a significant increase in overall survival in patients with newly diagnosed advanced BTC treated with nab-paclitaxel in combination with gemcitabine and cisplatin compared with gemcitabine/cisplatin alone (6), however, benefits were found for a subgroup of patients, and it would be of interest to identify markers to select those who would respond to this and other chemotherapy combinations.

Targeted therapy options for CCA and other BTCs are rapidly evolving. Over the last few years, the field has developed significantly, and new opportunities and challenges have arisen. With the more widespread use of molecular profiling, very relevant knowledge has been gained. We have now identified new targets of interest, such as murine double minute-2 (MDM2) amplifications, Ring Finger Protein 43 (RNF43) mutations and other aberrations
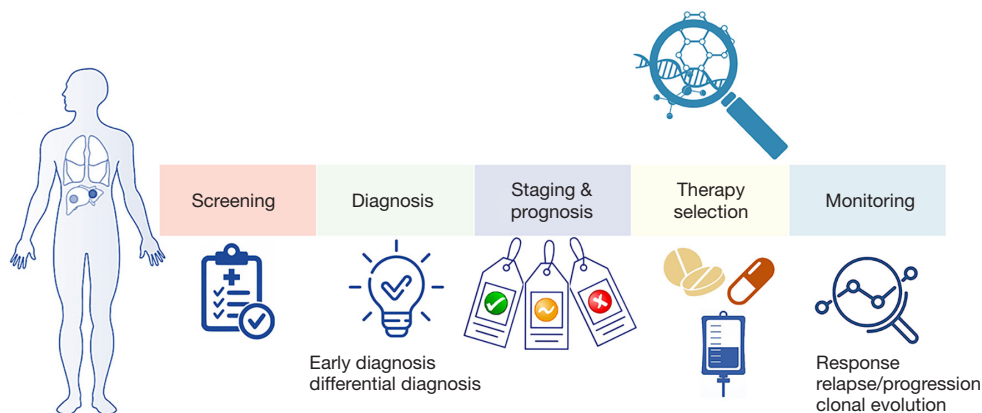
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Figure 1 Outline of the different types of biomarkers being investigated to improve the quality of life of patients with biliary cancer.

that, even if rare, could have a very significant impact for individual patients (7). We are also understanding better the potential association between genomics and patient phenotype, and interesting data have been reported for both isocitrate dehydrogenase (IDH) and the fibroblast growth factor receptor (FGFR) populations in these setting (8). Most importantly, we have now a much better understanding of the real prevalence of some of the molecular alterations. It is of relevance to highlight, for example, the fact that FGFR2 alterations, initially thought to be present in around 10–20% of iCCA (9), are far less frequent (around 9%) (7). This has very important implications at the time of further development of these compounds. We have, indeed, faced real challenges recruiting into first-line studies in the FGFR2-fusion positive population due to this lower-than-expected prevalence. As a consequence, some of the planned studies in the first-line setting (e.g., futibatinib and infigratinib) stopped recruitment due to low accrual, with pemigatinib being the only compound still under development in this setting (FIGHT-302; NCT03656536).

In terms of study design, most of these targeted therapies have been tested in second-line setting, within non-randomized phase II studies. Due to limited prevalence of these patient populations, it is challenging to gather confirmatory phase III data, and it is likely that in the coming future approvals based on basket studies without a control arm may need to be considered. Despite these, two things are important to highlight. First, randomized studies are not unachievable in CCA. In fact, we have the example of the ClarIDHy study, testing ivosidenib compared to placebo in the second-line setting for patients harboring an IDH1 mutation. Second, one of the

main challenges associated to non-randomized studies is the result interpretation. The fact that most targetable alterations are identified within the intrahepatic CCA (iCCA) population (10), together with the fact that iCCAs have a better prognosis compared to other BTCs, must be taken into account when interpreting outcome data, especially survival-based analyses (progression-free survival and overall survival).

In addition to new "settings" (such as the first-line), new and more specific compounds are also being developed. Third-generation FGFR inhibitors, such as futibatinib and RLY-4008, have reported response rates of around 40% and 80%, respectively (11,12). Bispecific HER2 antibodies have also reported higher response rate than those achieved with other HER2-targeted strategies (13).

One of the main challenges is access to testing and matched treatments for the identified alterations. A recent study by EORTC has highlighted this issue, showing that access to treatment remains challenging, especially in Europe (14). In this study, despite identifying a targetable alteration in around 35% of iCCAs, less than 10% were able to receive a tailored treatment for that alteration.

In the latest years, the use of immune-checkpoint inhibitors (ICIs), as single agents or in combinations with other drugs, has become a standard of care in various cancer types. However, early phase trials of pembrolizumab as single agent in previously treated BTC reported inconsistent results (15), and some combinations did not confirm their preliminary promising data (3). As pointed out by Munugala *et al.* (3), a clear benefit was observed only in patients with MSI-H/dMMR tumors, a characteristic observed in less than 5% of patients with BTC (16). Indeed,

with the exception of MSI-H/dMMR, no biomarkers were shown to be predictive of outcome on ICIs, and programmed cell death protein 1 ligand (PD-L1) expression did not show a consistent correlation with ICI activity in BTC patients (15).

More recently, the phase III TOPAZ-1 trial demonstrated the benefit of adding the PD-L1 inhibitor durvalumab to the combination of cisplatin and gemcitabine, setting the new first-line standard of care for patients with advanced BTC after more than 10 years of chemotherapy alone (17). The benefit of combining chemotherapy and immunotherapy has been confirmed by the very recently presented phase III KEYNOTE-966 trial that met its primary endpoint of improved overall survival with pembrolizumab plus cisplatin and gemcitabine compared to chemotherapy alone (18), providing a further immunotherapy option in this setting.

However, several open questions remain to be addressed. First, which patients are most likely to benefit from the combination of frontline immunotherapy and chemotherapy. The TOPAZ-1 study showed that some patients appear not to benefit from the combination of chemotherapy and durvalumab, while some patients show a long-term benefit. Therefore, we are in dire need of biomarkers for immunotherapy and ongoing translational studies are trying to answer this question. We need response/outcome biomarkers, resistance biomarkers, and we need to identify patients with long-term survival. CCA has been shown to be characterized by an immunosuppressive tumor microenvironment and its targeting may become a potential immunotherapy approach (19). Second, which patients might benefit from ICIs in combination with other agents in second line and beyond. In this setting, the LEAP-005 phase II study showed promising results with the combination of pembrolizumab and the multikinase inhibitor lenvatinib in previously treated patients (20). Also of interest is the possibility of combining immunotherapy with targeted agents given the good safety profile of ICIs and lack of overlapping toxicities, for example combining ivosidenib with immunotherapy could be a way to improve outcomes in patients with IDH1-mutant CCA. Pending predictive biomarkers, combining immunotherapy with other agents, chemotherapy or targeted agents, appears to be the simplest way to broaden the patient population who could benefit, as already shown in other cancer types. However, the ultimate goal should be to identify the best therapeutic option for each patient, and this goal cannot be separated from the identification of predictive biomarkers, not only for targeted agents, but also for immunotherapy.

As Munugala *et al*. (3) highlight, a better understanding of mechanisms of drug resistance in BTC could help to predict the response of each patient to the different therapeutic options and, therefore, to select the most appropriate treatment to improve survival outcomes. However, this is not straightforward because tumor cells continually develop complex resistance mechanisms to try to survive in the presence of anticancer agents. These mechanisms of chemoresistance include: (I) reduced drug uptake or increased drug efflux, (II) impaired metabolic activation/inactivation, (III) modifications of molecular targets, (IV) enhanced DNA repair capacity, (V) activation of signaling pathways associated with cell survival and proliferation, (VI) changes in tumor microenvironment, and (VII) epithelial-mesenchymal transition activation (21). Our understanding of these mechanisms is not yet complete, but there is evidence that they also contribute to the lack of response to targeted therapy and immunotherapy in BTC.

As mentioned, the field is evolving towards combination strategies with several therapies, with the field slowly moving from a "single" strategy to a "combination" strategy. In this sense, several things should be taken into account. First, it would be necessary to study the changes in the mechanisms of resistance that occur in tumor cells in the presence of various drugs to determine whether they are different. Second, given that tumor cells continuously develop new mechanisms to survive and adapt to the clinical challenge, it would be necessary to perform these analyses periodically to anticipate the next step and due to the challenges associated with obtaining tumor samples, the implementation of a minimally invasive liquid biopsy would be an optimal approach for monitoring CCA resistance in the near future.

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