More than shots in the dark: improving patient stratification to move closer to personalised therapies in intrahepatic cholangiocarcinoma

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Cholangiocarcinomas, the second most frequent hepatic tumour after hepatocellular carcinoma, make up around 2% of all gastrointestinal malignancies. It is believed that these tumours have been occurring more frequently recently, at least in Western countries, and that this is mostly due to an increase in intrahepatic cholangiocarcinoma (iCCA).[1] The combination of cisplatin and gemcitabine was established as the first-line therapy for patients with advanced cholangiocarcinoma for several years based on the findings of the ABC-02 trial. Recently, the phase III TOPAZ-1 and KEYNOTE-966 studies found a survival benefit with durvalumab or pembrolizumab in combination with gemcitabine and cisplatin, respectively.[2] In a real-world scenario, phase III TOPAZ-1 trial data were validated.[3] With very few clinical data, the relevance of second-line chemotherapy following progression is still up for debate. Fluorouracil and oxaliplatin regimen was recently reported by the ABC-06 study to be related with better overall survival in patients with advanced cholangiocarcinoma. With a 5-year survival rate of about 2%, traditional treatment used in advanced stages still produces disappointing results.

In this still devastating context, the use of next-generation sequencing (NGS) technologies has recently surpassed the use of conventional diagnostic methods, enabling extensive genomic profiling investigations of intrahepatic CCA and the identification of potentially targetable mutations. Another key aspect to enhance the prognosis of these patients is to identify in advance which patients will benefit from the available therapeutic options. With this in mind, in *Gut*, O'Rourke *et al* aimed to understand and predict the response of advanced iCCA patients to chemotherapy by employing NGS technology on tissue biopsies obtained prior to the initiation of treatment.[4] For this purpose, the authors identified two subgroups of patients with de novo advanced unresectable iCCA who, while having similar clinical features at diagnosis, responded extremely differently to chemotherapy: rapid progressors (RP) and long survivors (LS). Whole-transcriptome profiling of the bulk diagnostic biopsies allowed the identification of a new RNA-based gene expression signature associated with benefit from chemotherapy. Of note, in this cohort, the expression of genes related to gemcitabine uptake/metabolism or other established transcriptomic predictors of chemosensitivity in other cancers did not distinguish between RP and LS. These data establish the framework to develop a tool for clinical use that can identify which patients should be treated with chemotherapy and which patients should not, avoiding unnecessary toxicities and enabling earlier orientation towards alternative treatments instead (figure 1). Moreover, further transcriptomic profiling of geospatially macrodissected regions unveiled that the identified RPLS signature was specific to tumours, as negative in invasive fonts and non-malignant regions. Crucially, it was detected not only in tumour cores, but also in tumour stromal regions. This implies that biopsies rich in stromal content, even with few tumour cells, as could be the case in iCCA, can effectively function as a diagnostic matrix. However, a notable limitation is that the signature requires the analysis and interpretation of 504 genes; further optimisation is necessary to develop a clinical-grade test. Although future large-scale studies will be needed to validate their value, the present results have the potential to affect at several levels the management of patients with iCCA, a difficult-to-treat and deadly solid tumour. From a clinical standpoint, the identification of an RNA-based test, which may predict the response to complex treatment strategies, would have a highly positive impact on patient management in the direction of personalised medicine. A reliable RNA-based test would allow the clinician to tailor the treatment based on the likelihood of response, avoiding unnecessary side effects. Thus, as the authors point out, patients classified as LS by this new RPLS signature could quickly benefit from chemotherapy. Meanwhile, individuals with high RPLS scores would be prioritised for additional molecular profiling to assess potential alternative treatment options. From an economic point of view, limiting a treatment with a low possibility to be effective may clearly save resources to be dedicated to other aspects of the patient's care.

Importantly, the present study has also a high scientific value, as it aims to comprehensively characterise with multiple modalities the tumour and its microenvironment, elucidating critical immunoregulatory capabilities of the liver stroma involving the interaction between tumour myeloids and tumour T cells. This original investigation may not only provide information on the response to therapy, but is also likely to identify novel pathways and/or targets which may be further investigated in translational studies. Among multilayered mechanisms contribute to RPLS-associated chemoresistance, metabolic reprogramming is associated with immunosuppressive microenvironments, and myeloid cells potentially establish a metabolically initiated and competitive tumour niche.

Currently, immune checkpoint inhibitors are under investigation and the addition of durvalumab or pembrolizumab to standard chemotherapy recently demonstrated a survival benefit as first-line therapy. However, these results were obtained in an unselected population, and no information is available on the tumour characteristics which could predict the response to immunotherapy. This aspect could be considered to further develop O'Rourke's study to make this type of cancer more treatable in the next years. In this context, the authors illustrated that tumour-induced immune tolerogenicity is a distinguishing feature of RP phenotypes. This implies that the immune evasion mechanisms used by RP-like tumours could

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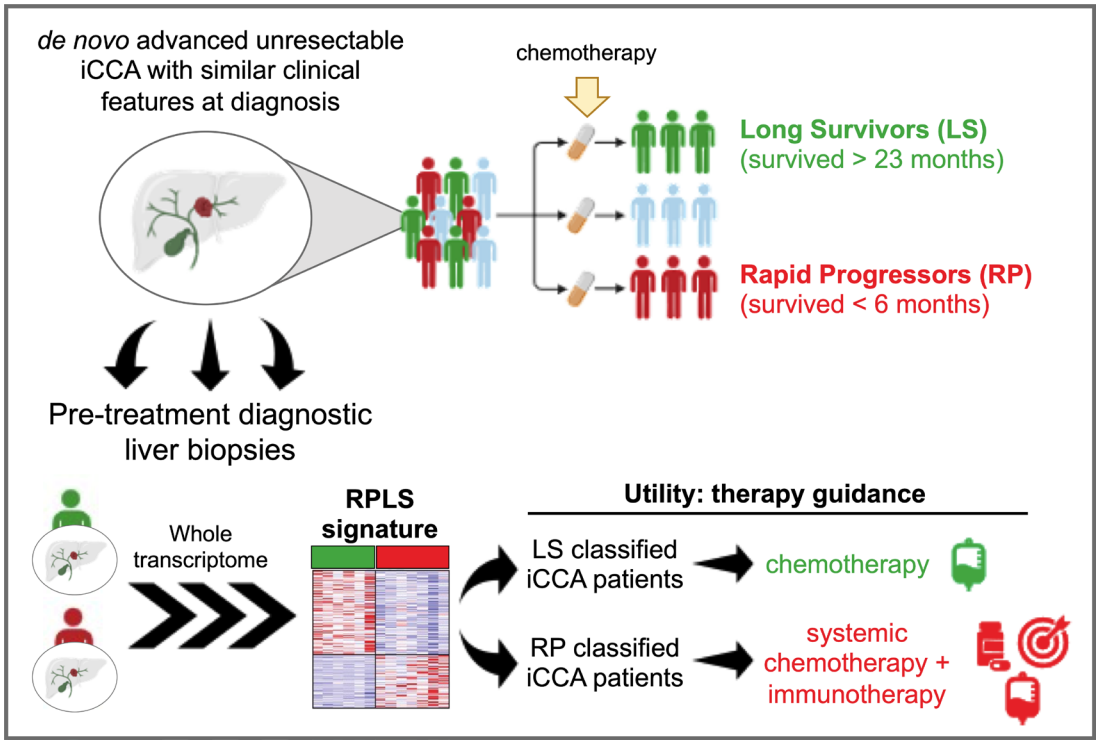

Figure 1 The figure highlights the importance of the RPLS signature in predicting therapy response at time of diagnose. iCCA, intrahepatic cholangiocarcinoma. Created with BioRender.com.

render them more susceptible to checkpoint inhibitors in comparison to LS-like tumours. Simplifying the scenario, this RPLS signature could potentially serve as a novel tool for predicting treatment response, thereby justifying the choice of chemotherapy for LS-like tumours or immunotherapy for RP-like tumours, among other alternatives, at the time of diagnosis.

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