The evolving landscape of precision medicine in primary liver cancer

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The incidence of primary liver cancer (PLC) is rising faster than any other malignancy in the USA and is estimated to result in over 31,000 deaths in 2019 [1]. PLC poses a unique challenge in that the majority of patients suffer from both their malignancy and underlying liver damage which is the inciting factor for their hepatocarcinogenesis. Viral infections such as Hepatitis B and C, lifestyle choices such as heavy alcohol use and inherited genetic disorders such as primary biliary cirrhosis can all lead to underlying liver cirrhosis leaving the patient vulnerable to malignancy and without aggressive treatment options.

There are multiple histologic subtypes which comprise PLC but by far the two most common are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). Interestingly, while historically treated as two distinct malignancies, there is a growing body of evidence that they may be more alike than previously thought. Classically it was believed that iCCA arose from cholangiocytes, and while the origins of HCC remained more elusive it was hypothesized that hepatic stem cells in addition to hepatocytes were implicated. More recent work reveals that both malignancies could originate from hepatocytes and more strikingly, in certain subsets of patients, share a common molecular subtype [2–4]. These commonalities shed light on the potential drivers of hepatocarcinogenesis and are the first steps of novel targeted therapies. With a more thorough understanding of these tumors, directed personalized care is possible.

Where are we?

Our current diagnostic and treatment paradigm in PLC is based on three key factors: tumor morphology, distant metastasis and underlying liver dysfunction. Unfortunately, the majority of patients are diagnosed when tumors are large, have metastasized or their liver disease has advanced. In these patients, only a few systemic therapies are available, and none of them are particularly efficacious. In the first line, HCC patients receiving systemic sorafenib and iCCA patients receiving combination cisplatin and gemcitabine both have a median survival of less than 1 year [5,6]. To date multiple Phase III trials with small molecules such as sunitinib, brivanib, linifanib and erlotinib have failed to improve on this dismal prognosis [7]. In addition, the few positive trials for second line agents such as, regorafenib, lenvatinib and carbozantinib have all resulted in a survival advantage of only a few months [8]. As the field of oncology progresses into the immunotherapy era, nivolumab, a PD-1 immune checkpoint, is the first to garner US FDA approval for PLC. While only a 20% objective response rate was noted in the CheckMate 040 trial, there were a handful of complete responders offering hope for the future of immunotherapy and PLC [9]. Regardless of intervention – albeit surgery, chemotherapy, targeted therapies or immunotherapy – they all represent a one-size-fits-all mentality. PLC patients are treated as a homogeneous group stratified by only visible tumor

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characteristics. Given the relative rarity of the disease, this approach makes practical trial design sense, but while other malignancies have seen unprecedented drops in mortality, PLC has found itself on the outside looking in.

Why are we failing?

Dr Blake Cady, a prominent surgical oncologist, stated "Biology is King; selection of cases is Queen and the technical details of surgical procedures are princes and princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail, although with some temporary apparent victories." [10]. Despite its truth, more than 20 years later we have yet to leverage our biologic understanding of PLC to a therapeutic advantage. While trial design is tumor histology centric, it fails to account for the vast biologic differences as a result of tumor heterogeneity. PLC heterogeneity begins with the diverse array of etiologies which drive hepatocarcinogenesis and continues down to the individual cells that comprise the tumors and their microenvironments. PLC intertumoral heterogeneity is evident by unique molecular signaling pathways which result in subclassification of tumors that although visually similar, are actually very different [4]. Further, single cell sequencing technology now allows characterization of not only the difference between tumors but also within the tumor itself or intratumoral heterogeneity. From this work we now understand that within a tumor there are also distinct molecular signatures, specifically of hepatic cancer stem cells, which contribute to carcinogenesis [11]. Lastly, the very interventions that we rely on to treat the tumor may further promote diversity by facilitating a tumor microenvironment with resource limitation and immune predation thus driving evolutionary selection pressures promoting diversity [12].

Improved outcomes through precision medicine

Next generation sequencing (NGS) highlights tumor molecular heterogeneity, challenging the one-size-fits-all treatment paradigm yet it also offers insights into potential vulnerabilities that can be exploited. Precision medicine is the concept that through a multiomics approach, patients are no longer treated solely by the histology of their tumor, but instead through actionable targets specific to their tumor biology. NGS panels such as MSK-IMPACT represent a multifunction approach that aims to improve cancer care and research. First, the data gathered from these tumors is publicly available, which gives researchers the opportunity to answer key translational questions which can only be accomplished with clinical samples. For patients, molecular profiles with potentially actionable targets are provided, which can guide clinical decision making. In the original MSK-IMPACT study, 36.7% of all patients had mutations which could potentially be targeted with currently approved agents regardless of histology [13]. More impressively, when tumors such as gastrointestinal stromal tumors, thyroid cancer, breast cancer and melanoma were evaluated more than 50% had potentially actionable mutations [13]. Finally, omics profiling may provide greater access to clinical trials. In the same MSK-IMPACT study, 11% of patients were enrolled in genomic alteration-specific trials encompassing more than 50 different genes, a concept known as basket trials [13]. Classical clinical trial design is focused on specific cancer histology and commonly is specific to a patient population. Conversely, basket trials are designed to capture all patients with a specific genetic mutation regardless of histology, age or underlying etiology. The largest of these trials, the National Cancer Institute's Molecular Analysis for Therapy Choice (MATCH) trial has already enrolled over 6000 patients with a plan to have nearly 40 mutation-specific treatment arms [14]. Another much smaller basket trial design has already produced positive results and has resulted in the approval of larotrectinib, a highly selective *TRK* inhibitor, for patients with *TRK* fusion cancer which highlights the potential to target biology rather than histology [15].

A major obstacle for the implementation of precision medicine in PLC is the reluctance to perform diagnostic biopsies. Currently, none of the major sources of guidelines recommend the routine use of biopsies in PLC. It is therefore unsurprising that in the 10,000 patient MSK-IMPACT trial, PLC represented just 1% of patients [13]. Diagnostic imagining when combined with the tumor marker, α-fetoprotein, are both incredibly sensitive and specific for HCC. In addition, there has classically been a debate over the risk of tumor seeding of the biopsy tract outweighing the diagnostic information garnered. This argument is currently a subject of debate as prospective tumor seeding studies have shown no statistically significant risk debunking previous retrospective studies such as Silva *et al.*, which had reported tumor seeding as high as 2.7% [16,17]. In addition, while biopsies offered little histologic information which would help guide clinical decision making, as previously mentioned, the wealth of molecular information that can be obtained through NGS is priceless. Additionally, given the knowledge that therapy influences clonal evolution, biopsies when there is progression can further guide second- and third-line treatments.

An emerging technology which may represent an alternative to conventional biopsy is the concept of liquid biopsy. In this approach circulating tumors cells (CTCs), DNA or RNA can be detected from a sample of the patient's peripheral blood. Ogle *et al.*, using common HCC markers and flow cytometry, were able to identify CTCs in 45 of 69 patients with HCC and demonstrated that the absence of CTCs confirmed a significant survival advantage [18]. In addition, multiple groups have demonstrated that through the utilization of single cell sequencing technology, NGS of CTCs is possible [19]. While exciting, this is an area that will need further research and development. Multiple studies suggest that the absolute number of CTC is rather low thus necessitating improvements on current isolation techniques [20]. In addition, the low yield requires improvement in current mathematical models for bioinformatic analysis of the data. With continued translational research and clinical trials this technology has the potential to be a readily available, noninvasion test which may help guide individualized therapies.

Conclusion

The field of oncology and cancer research is changing. As our understanding of the underlying biology of the disease improves, the one-size-fits-all treatment model has been exposed as inadequate. PLC is among the hardest to treat malignancies and as such carries one of the worst prognoses. While there are many challenges to overcome, our understanding of tumor heterogeneity and the technologic advances of NGS are slowly making precision medicine a reality. Precision medicine promises personalized care directed at the underlying machinery of each patient's tumor with the goal of improved outcomes for all.

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