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Liver Field during Immunotherapy of Hepatocellular Carcinoma: Some Like It Hot

Pfister D, Nunez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 2021;592:450–456.

In 2008, the approval of the multikinase inhibitor sorafenib opened the door to the systemic therapy of hepatocellular carcinoma (HCC) and started intense investigations on prognostic factors that might help refining the design of registration trials and to optimize the utilization of new therapeutic regimens. Along this line, particular attention has been paid to the identification of survival predictors in patients exposed to the newly developed anti-HCC molecules. In sum, these crystallized into patient stratification based on the presence or absence of extrahepatic spread, macrovascular invasion and elevated α-fetoprotein levels, but leaving it debated whether the outcome of therapy could also be influenced by etiologic risk factors (Nat Rev Gastroenterol Hepatol 2021;18:293–313).

Indeed, in the exploratory subanalysis of the registration trial SHARP, in which sorafenib was shown to outperform placebo across diverse etiologies, hepatitis C virus (HCV)–infected patients treated with sorafenib showed longer survivals, less tumor progression and better disease control rates than those infected with hepatitis B virus (HBV) or with alcoholic liver disease (J Hepatol 2012;57:821–829). Further exploring the relationship between survival advantage and disease etiology, an individual patient data meta-analysis of 3 registration trials that singularly failed to demonstrate non inferiority or superiority of alternative regimens versus sorafenib, supported the contention that the beneficial impact was largely confined to HCV infected patients who tested negative for HBV (J Clin Oncol 2017;35:622–628). However, the mechanism underpinning the improved outcomes conferred by sorafenib in HCV-infected patients remained largely unexplained (J Clin Oncol 2017;35:622–628). Challenging the robustness of these conclusions, the trials were not randomized in terms of etiology, a methodologic flaw that caused the cohorts to be numerically unbalanced and heterogeneous in terms of performance status. Further, there was no mention on the proportion of HBV-infected patients receiving effective antiviral therapy, not to speak about the absence of patient evaluation for the presence of nonalcoholic fatty liver disease (NAFLD). By the same token, the relationship between HBV infection and anti-HCC activity that surfaced in a post hoc analysis of the registration trial that led to the approval of lenvatinib and cabozantinib as first and second line options, respectively, also requires attention. In addition, the impact of etiology on anti-cancer activity of the second line drugs regorafenib and ramucirumab has remained undisclosed.

Further undermining the robustness of some of these subanalyses, patients with alcoholic liver disease were classified together with those with NAFLD, a condition that recently emerged as a potential confounder in trials evaluating the anti-HCC activity of immune check point inhibitors (Nature 2021;592:450–456). In a sensitivity analysis of IMbrave150 that led to the approval of the first-line combination of atezolizumab plus bevacizumab, patient survival was significantly extended in the subset with HBV- or HCV-related cancers only, but not in those with metabolic/toxic liver disease. These findings were confirmed by a meta-analysis of patients enrolled into IMbrave150 and 2 registration trials evaluating nivolumab and pembrolizumab therapy of HCC and by a post hoc analysis of 2 real-life cohorts dosed with programmed death-1 (PD-1) and its ligand targeted immune therapy (Nature 2021;592:450–456; J Clin Oncol 2021;39:267–267). Specifically, Pfister et al demonstrated that in experimental models and in the liver samples of patients with NAFLD there is a progressive accumulation of exhausted resident cytotoxic T lymphocytes ($CD8^+PD1^+CXCR6^+$ cells), which not only show impaired immune surveillance activity, but also contribute to liver damage progression (Nature 2021;592:450–456). As a consequence, in this liver field setting featuring excessive fat accumulation and lipotoxicity, treatment with anti–PD-1 immune checkpoint inhibitors did not prevent, but rather exacerbated hepatic carcinogenesis. Promotion of

carcinogenesis mediated by $CD8^+PD1^+$ lymphocytes could be prevented by $CD8^+$ cells depletion or inhibition of tumor necrosis factor, lending further support to a main role of immune system dysregulation in this process (Nature 2021;592:450–456).

Finally, the authors showed that in an individual patient data meta-analysis of 3 registration trials of PD-1 and PDL-1 inhibitors for the treatment of advanced HCC, patients with nonviral HCC (mostly affected by NAFLD and alcoholic fatty liver disease) showed a lower survival rate as compared with those with chronic viral hepatitis, in keeping with a detrimental impact of fatty liver on the efficacy of this therapeutic approach (Nature 2021;592:450–456). Altogether, these findings fueled the suspicion that enrolment of patients with metabolic related HCC might have partially accounted for the failure of previous registration trials of PD-1 and PDL-1 targeted immunotherapy.

Comment. NAFLD, which is defined by increased hepatic fat accumulation not accounted for by at-risk alcohol intake or other hepatotoxic factors, is most frequently associated with dysmetabolism and it has become the most common chronic liver disease worldwide; it affects nearly 30% of adults in the general population (Nat Rev Gastroenterol Hepatol 2018;15:11–20). NAFLD can be complicated by nonalcoholic steatohepatitis, which is a potentially progressive condition and is already among the leading etiologies of HCC (Nat Rev Gastroenterol Hepatol 2019;16:411–428). Increasingly robust data show that, among individuals with NAFLD, slightly less than 1 case in 2 develops HCC independent of cirrhosis (Nat Rev Gastroenterol Hepatol 2019;16:411–428), suggesting that hepatic fat directly promotes carcinogenesis, independent of the cirrhotic milieu. The result is frequently a delayed diagnosis at an advanced stage, leading to a poor prognosis.

Two studies recently published back to back now shed light on the dysregulation of immune system, and in particular of lymphocytic cytotoxic response, in metabolic fatty liver disease (Nature 2021;592:450–456; Nature 2021;592:444–449), which is consistent with epidemiological and new genetic data that the mechanism driving hepatic carcinogenesis in NAFLD is partially independent of fibrogenesis (J Hepatol 2021;74:775–782). Indeed, in experimental NAFLD metabolic cues related to obesity, namely, increased IL-15, led to liver recruitment of $CD8^+$ T cells via up-regulation of the chemokine receptor CXCR6, which rendered these resident lymphocytes susceptible to metabolic stimuli (Nature 2021;592:444–449). Products of fatty acids metabolism would next trigger autoaggression and the killing of hepatocytes, independent of antigen presentation (Nature 2021;592:444–449).

Interestingly, CXCR6 expression on T cells and natural killer cells alike is typical of resident immune cells that normally populate several other organs beside the liver (J Leukoc Biol 2004;75:267–274) and may be specifically recruited in inflamed tissues. A typical example of enhanced CXCR6 expression on natural killer cells and CD8 T cells is severe coronavirus disease 2019, during which these cells home to the lung to perform effector function, where CXCL16, the ligand of CXCR6, is highly expressed (Nat Commun 2019;10:3841). Autoimmune $CD8^+CXCR6^+$ T cells may also be recruited to the liver, where CXCL16 is also expressed and its down-modulation decrease liver macrophage infiltration and steatohepatitis in an animal model (PLoS One 2014;9:e112327).

Of note, Pfister et al observed that, in NAFLD, $CD8^+CXCR6^+$ T cells displayed an apparently contradictory phenotype characterized by co-expression of granzyme B and PD-1, which are associated with effector function and exhaustion, respectively (Nature 2021;592:450–456; Nat Rev Gastroenterol Hepatol 2018;15:11–20). The mechanisms driving T-cell exhaustion have been recently clarified and can be largely attributed to continuous antigen exposure together with hypoxic conditions in the microenvironment, leading to profound mitochondrial dysfunction (Nat Immunol 2020;21:1022–1033). The elimination of the persistent stimulus will rescue terminally exhausted T cells whereas, unfortunately, progenitor exhausted $CD8^+$ T cells, which retain the ability to secrete inflammatory cytokines, persist, bearing a molecular scar of exhaustion (Nat Immunol 2021;22:229–239). Interestingly, the $CD8^+CXCR6^+$-T cell subset was highly enriched in the liver of patients with severe NAFLD, especially within NAFLD–HCC nodules, and expressed high levels of PD-1.

The most remarkable finding, however, was that, in experimental models of NAFLD, PD-1 blockade, a mechanism exploited by immune checkpoint inhibitors to restore tumor immune surveillance, led to an expansion of intratumoral T cells, exacerbating liver damage and regeneration without being able to induce tumor regression. Paradoxically, preventive treatment with PD-1 and PDL-1 inhibitors led to an increase in the number and size of HCCs (Nature 2021;592:450–456). Therefore, the presence of NAFLD and lipotoxicity seems able to thwart the T-lymphocyte tumor infiltration ("hot tumor") and immune response against HCC, generally associated with a favorable prognosis and response to immune therapy (Gut 2021;70:204–214), bending it to become maladaptive and favor tissue damage and tumor growth.

Recent human genetic data independently strengthened these findings, buttressing their translational relevance, by showing that inherited predisposition to higher PD-1 expression in T cells and monocytes due to variation at the *PDCD1* locus encoding for PD-1 itself may increase the risk NAFLD-HCC (Cancers (Basel) 2021;13:1412–1429). However, the impact of *PDCD1* variation on the response to PD-1 and PDL-1 inhibitors remains to be ascertained.

Although aligning with the contention that antitumor surveillance is impaired in NAFLD livers as a consequence of a profound derangement of intrahepatic immunity, these observations temper our expectations for regimens based on immune checkpoint inhibitors to be a real therapeutic breakthrough across all HCC etiologies, raising the question as to whether next trials of anti-HCC molecules should be designed with patient randomization by etiology. As a matter of fact, Pfister and associates should be commended

for raising the attention on liver disease etiology being a potential modifier of response to immune check point therapy of HCC (Nature 2021;592:450–456), even more so in an era of raising incidence of metabolic related liver cancer that is prone to escape early diagnosis and thereby is often detected at advanced stage when systemic therapy is the only remedy (Nat Rev Gastroenterol Hepatol 2019;16:411–428). Although alcoholic liver disease and NAFLD share a number of pathogenic mechanisms leading to progressive liver injury and genetic drivers such as the *PNPLA3* variant (JHEP Rep 2021;3:100284), the relationship between etiology and response to immune checkpoint inhibitors needs to be reevaluated in larger cohorts well-characterized for both alcohol intake and metabolic risk factors, after accurate stratification for survival predictors like extrahepatic spread, portal vein invasion and α-fetoprotein. Although the currently available findings provide some evidence against the use of checkpoint inhibitors in the setting of HCC emerging in the context of NAFLD, future studies should evaluate the possibility to rescue terminally exhausted T cells by pharmacologic approaches that, for example, alleviate lipotoxicity and mitochondrial stress, or as suggested by Pfister et al (Nature 2021;592:450–456), by directly targeting immune cell subsets.

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