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Biochemical predictors of response to immune checkpoint inhibitors in unresectable hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) represents the most commonly diagnosed liver cancer worldwide, and the overall survival of patients with unresectable disease is poor. In the last five years, immune checkpoint inhibitors (ICIs) have revolutionized the treatment scenario of several hematological and solid tumors, and these agents have been actively explored in unresectable HCC. Firstly, promising findings of phase I and II clinical studies reporting durable responses and a tolerable safety profile have led to the assessment of ICIs as single agents in phase III clinical studies; however, the latter have provided controversial results, and the activity of ICI monotherapy seems limited to a small subgroup of patients. Conversely, the IMbrave150 trial recently showed that, among patients with previously untreated unresectable HCC, treatment with atezolizumab plus bevacizumab resulted in significantly longer overall survival and progression-free survival compared to sorafenib monotherapy. In addition, the activity of several other ICIs is under investigation, as combination immunotherapy as well as combinations of immunotherapy with antiangiogenic agents. Nonetheless, there are currently no validated predictive biomarkers able to guide treatment choice in this setting, where the identification of specific predictors of response to ICIs represents a major challenge. In this review, we aim to provide a critical overview of recent evidence on biochemical predictors of response to ICIs in patients with unresectable HCC, especially focusing on PD-L1, TMB, MSI, and other emerging biomarkers.

Introduction

Hepatocellular carcinoma remains one of the most frequent solid tumors worldwide, accounting for more than 80% of all primary liver malignancies and representing the fourth case of cancer-related death throughout the world [1-3]. Unfortunately, according to estimates by the World Health Organization (WHO), at least one million patients will die from HCC over the next ten years [1, 2]. Infections with hepatitis viruses, especially HBV and HCV, have been historically associated with the onset of HCC and are the most frequent risk factors [4]; however, several other factors have been related to HCC occurrence, including environmental toxins (e.g., aflatoxin), liver cirrhosis, smoking, genetic disorders, and non-alcoholic fatty liver disease (NAFLD), with the latter recently becoming one of the main etiological factors in most Western countries (Fig. 1) [5, 6].

Treatments for HCC are stratified according to the stage of the disease and the concomitant liver dysfunction, with surgery remaining the mainstay of cure in early stages [7, 8]. Notably enough, the last five years have witnessed an outstanding development of novel therapeutic options for patients with advanced HCC, including multikinase inhibitors targeting vascular endothelial growth factor receptor (VEGFR) 1, VEGFR2, and VEGFR3, platelet-derived growth factor receptor (PDGFR) alpha and beta, rapidly accelerated fibrosarcoma (RAF), and several other kinases, as well as immune-checkpoint inhibitors (ICIs) and combinations of both strategies [9, 10]. As regards the former, following the results of phase III randomized controlled trials, four targeted therapies have been approved for treatment of unresectable HCC [11]. In particular, these treatments include lenvatinib in treatment-naïve HCC and cabozantinib, ramucirumab, and regorafenib in previously treated patients whose disease progressed following first-line systemic therapy [12-15].

Concurrently, notable advances in the comprehension of biology and immunogenicity of cancer have been achieved over the last years, leading to the extensive evaluation of ICIs in hematological and solid tumors [16-19]. In particular, antibodies blocking the interactions between Programmed Cell Death Protein 1 (PD-1) and Cytotoxic

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T-Lymphocyte Antigen 4 (CTLA-4) have been successful in medical treatment of several malignancies, and thus, the treatment landscape for a wide range of cancers has shifted dramatically over a relatively short period of time, following the results of landmark clinical trials in this setting (Fig. 2) [20-23]. However, although ICIs have revolutionized anticancer treatment, a non-negligible proportion of patients do not achieve durable responses, and variation in the response rate to these agents have strongly encouraged the active search for reliable biomarkers which could predict clinical outcomes [24-26].

As previously stated, the role of ICIs in unresectable HCC has been recently explored in several phase I to III clinical trials, reporting landmark as well as controversial results [27]. In fact, monotherapy with ICIs has shown limited efficacy, with this strategy appearing to be beneficial in a limited subgroup of HCC patients [28, 29]. For example, the CheckMate-459 phase III trial comparing nivolumab (240 mg every two weeks) versus sorafenib as front-line treatment did not reached its primary endpoint, since median overall survival (OS) was 16.4 and 14.7 months in the experimental and the control arm, respectively (Hazard Ratio [HR] 0.85, 95% Confidence Interval [CI], 0.72–1.02; $p = 0.0752$) [29]. Additionally, overall response rate (ORR) was 15% in the nivolumab arm and 7% in patients receiving sorafenib [29].

Conversely, the 2020 saw the publication of the highly anticipated results of the IMbrave150 trial [30]; in this phase III study, 501 treatment-naïve advanced HCC patients were randomly assigned to receive atezolizumab (1200 mg every three weeks) plus bevacizumab (15 mg/kg every three weeks) ($n = 366$) or sorafenib monotherapy ($n = 165$), with OS and independent review facility-assessed progression-free survival (PFS) assessed as primary endpoints [31]. At the time of the primary analysis, median PFS was 6.8 months in the combination arm and 4.3 months in the sorafenib group (HR 0.59, 95% CI, 0.47–0.76; $p<0.001$) [31]. Of note, 67.2% (95% CI, 61.3–73.1) of patients in the atezolizumab-bevacizumab and 54.6% (95% CI, 45.2–64.0) in the sorafenib group were alive at 12-month follow-up (HR 0.58, 95% CI, 0.42–0.79; $p<0.001$) [31]. Moreover, the combination of atezolizumab plus bevacizumab resulted in a superior time to deterioration of patient reported quality of life and functioning compared to sorafenib monotherapy (11.2 months in the experimental arm and 3.6 months in patients treated with sorafenib, HR 0.63, 95% CI, 0.46–0.85) [30, 31]. In terms of safety, grade 3 or 4 toxicities were observed in 56.5% and 55.1% of patients receiving atezolizumab plus bevacizumab and sorafenib, respectively. In addition, patients treated with atezolizumab-bevacizumab reported pain, fatigue, diarrhea, and appetite loss in a lower proportion compared to sorafenib. Notably enough, the trial has represented something historical for the HCC medical community, being the first positive study over the last fifteen years to show an OS and PFS benefit in treatment-naïve patients for the experimental arm compared to the standard of care sorafenib [30, 31].

Although the results of the IMbrave150 have marked an important step forward in the medical treatment of advanced HCC and recent years have seen the approval of ICIs in this setting, several questions remain. Among these, a large number of patients with advanced disease do not obtain clinical benefit and/or do not achieve durable responses – thus, suggesting the need of identifying reproducible and reliable predictive biomarkers to guide treatment choice in HCCs receiving ICIs, as monotherapy or in combination with other anticancer agents [32, 33].

Since the mechanisms behind the different responses to ICIs among advanced HCC patients are far from being fully elucidated, in this review we outline and critically discuss potential biomarkers predictive of response to ICIs in this setting.

PD-L1 expression

The evaluation of PD-L1 expression probably represents the most commonly used biomarker in predicting clinical outcomes of cancer patients receiving ICIs, since PD-L1 has been associated with response to PD-1/PD-L1 inhibitors and better survival in several tumor types [34-36]. However, it is also well-known that a wide range of issues exist in the evaluation of PD-L1 expression, including the use of different antibody clones and cut-off scores to define PD-L1 positivity or negativity, as well as the expression of PD-L1 not only on tumor cells but also on immune infiltrating cells [37-39].

As regards the specific setting of ICIs for unresectable HCC, PD-L1 expression detected by using immunohistochemistry does not reproducibly correlate with the treatment response to ICIs, as monotherapy or in combination with other agents. In fact, the predictive value of PD-L1 is still unclear, with response rates consistent across all patients, regardless of PD-L1 expression [40]. For example, in the phase I/II CheckMate-040 trial investigating the role of nivolumab in HCC patients intolerant or refractory to sorafenib, PD-L1 expression was retrospectively evaluated [41]. This analysis on 174 HCCs for which PD-L1 expression was available used the cutoff of 1% of tumors cells expressing PD-L1; of note, responses were not statistically significantly associated to PD-L1 positivity or negativity, since overall response was observed in the 19% and the 26% of PD-L1<1% and PD-L1≥1% patients, respectively [41]. Additionally, the negative predictive value of the tests performed to assess the correlation between antitumor response and PD-L1 expression was often poor, with these studies which were not able to discriminate between non-responders and responders.

In terms of prognostic value, high PD-L1 expression has been suggested to be associated with lower survival and worse clinical outcomes in patients with advanced HCC [42]; more specifically, higher aggressiveness has been observed in those HCC patients whose disease showed high PD-L1 expression by intratumoral inflammatory as well as neoplastic cells [42].

In summary, further blood-based or tissue biomarker analysis need to be conducted in order to identify the real role of PD-L1 in this setting, and if this parameter could help to determine the subgroup of patients that would benefit most from ICIs [43]. In fact, current evidence suggests that if on the one hand some trials observed that high PD-L1 expression could be associated with poor outcomes, its predictive role remains elusive, as proven by treatment responses highlighted both, in patients with low or no expression of PD-L1 as well as in PD-L1 positive HCCs.

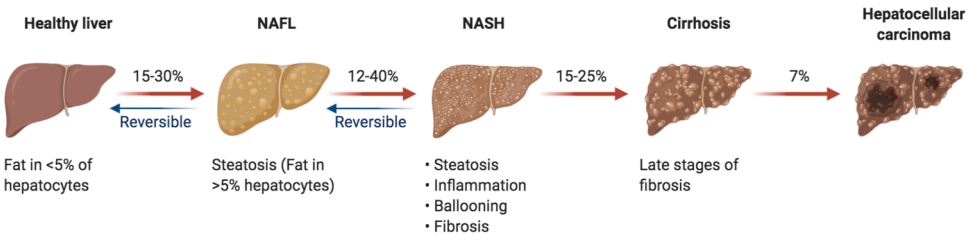

Fig. 1. Progression of non-alcoholic fatty liver disease (NAFLD). A range between 15 and 30% of patients presenting with liver steatosis progress to NAFLD and the 12–40% of NAFLD patients develop steatohepatitis. The subsequent steps are represented by liver cirrhosis and, in the 7% of cases, hepatocellular carcinoma (HCC). *Abbreviations: HCC: hepatocellular carcinoma; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis.*

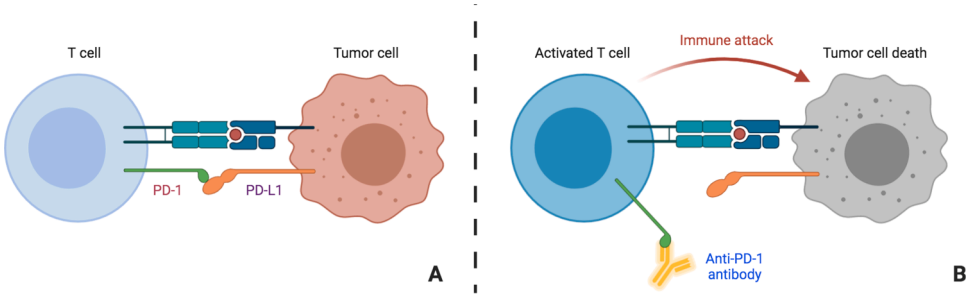

Fig. 2. Schematic figure representing the action of immune checkpoint inhibitors (ICIs) against tumor cells. In particular, immune checkpoint inhibits T-cell activation (Fig. 2A), while PD-1 inhibitors lead to T cell activation, enhancing the immune system response against cancer cells (Fig. 2B). *Abbreviations: PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1.*

TMB and MSI

Tumor mutational burden (TMB) – frequently defined as the overall number of somatic non-synonimous mutations per megabase highlighted in cancer cells - is another promising biomarker which has been tested in a wide range of tumor types, where several studies have observed an association between TMB and more favorable responses to ICIs [44-46]. However, although TMB has been suggested to be a potential biomarker that could identify those cancer patients who are more likely to benefit from immunotherapy, its role has not been prospectively validated.

As regards HCC, it is worth noting that median TMB has been reported to be around 4–5 mutations / megabase, with approximately the 5% of all HCC samples presenting more than 10 mutations / megabase [47]. However, as in the case of PD-L1 expression, a wide variability in terms of methods and kits used for the evaluation of TMB has been reported, and thus, the clinical value of this assessment should be interpreted with caution [48]. In fact, the clinical value of TMB in HCC is still under debate, since most data derive from studies with small sample size and remarkable selection bias. In addition, variations according to ethnicity have been also described in HCC, as suggested by a recent report by Tang and colleagues, which observed higher TMB in Chinese patients with HCC compared to Western subjects, with proportions of 9.3% and 1%, respectively [49].

In addition, TMB has been also assessed in concert with microsatellite instability (MSI), another potentially meaningful predictive biomarker of response to immunotherapy which has been strictly associated to defective mismatch repair system [50-52]. In fact, MSI hesitates in the accumulation of random mutations and the subsequent neoantigen formation; these processes lead to activation of T cells and the expression of inflammatory cytokines, thus enhancing cancer susceptibility to immunotherapy [50-52]. Notably enough, MSI high status (MSI-H) is considered a quite unusual finding in HCC, with less than 3% of patients observed to be MSI-H [53-55]. A recent study by Ang and colleagues analyzed 755 HCC specimens through comprehensive genomic profiling in order to identify predictive biomarkers of response to ICIs [56]. Of note, only the 0.2% of cases presented MSI-H and TMB high, suggesting that “hypermutated tumor phenotypes” are rare in HCC – in contrast to what has been observed in other tumor types [56-58]. According to the results of this study, TMB was 4 mutations / megabase, with only the 0.8% of HCC patients presenting high TMB [56]; lastly, the authors explored the relationship between potential predictive biomarkers and response to ICIs in 17 HCC patients, observing a complete response to the PD-1 inhibitor nivolumab in one HCC patient with microsatellite-low and TMB high (15 mutations / megabase) [56].

Overall, although TMB and MSI are considered useful as agnostic histologic indicator to select responders to ICIs, their role in HCC remains unclear, with several methodological questions needing to be addressed [56, 59]. A recently published report by Wong and colleagues focused on some of these issues since the authors tried to evaluate TMB in 29 HCC patients through targeted next-generation sequencing on fresh and archival samples [59]. Of note, fresh samples were shown to present lower TMB compared to archival ones (median 2.51 mutations / megabase and 958.39 mutations / megabase, respectively), and appeared to be the optimal source of tumor DNA for TMB evaluation [59].

DDR and other gene alterations

In recent years, the molecular landscape of several solid tumors has begun to emerge, offering clinicians and researchers an unprecedented landscape and marking the start of a new era [60-64]. Accordingly, molecular profiling has become increasingly significant over the past decade and has led to the identification of gene alterations which have been associated to response to ICIs [65-68]. As regards HCC, recent studies performing next-generation sequencing have highlighted the presence of somatic mutations in Epidermal Growth Factor Receptor (EGFR), TP53, FGFR, MET, PTCH1, PTEN, KRAS, NRAS, HRA, SMO, and DDR2, and these mutations have been suggested to have the potential to affect response to immunotherapy [69]. Additionally, also germline mutations may be involved in tumor response to ICIs, as suggested in the case of Janus-Associated Kinase (JAK) and Wnt / β-catenin signaling pathway. As regards the former, loss-of-function mutations in JAK1/2 have been associated to primary resistance to ICIs, while conversely, JAK2 amplifications seems to enhance responses to immunotherapy [70-72]. As regards the latter, preclinical models have identified the key role played by β-catenin in promoting HCC cell survival by supporting EGFR signaling in the early phases of carcinogenesis, while Wnt signaling is involved in escaping immune surveillance [73-75]. And on that note, a landmark study by Harding and colleagues used next-generation sequencing in patients with advanced HCC, trying to link this technique to everyday clinical practice and to identify those HCC patients which are more likely to benefit from systemic therapies [76]. In particular, 31 subjects were treated with heterogeneous immunotherapeutic agents and schedules (such as anti-PD-1 monotherapy, anti-CTLA-4 monotherapy, anti-LAG3, etc.), ten of which presented Wnt / β-catenin mutations [76]. Among this specific subgroup of Wnt / β-catenin-mutated patients, no response to ICIs were observed, while the 50% of wild-type HCCs responded to immunotherapy [76]. Since these aberrations are not rare in HCC, although these studies are still preliminary, next generation sequencing could provide useful information in predicting response or resistance to ICIs [70, 76].

Lastly, DNA damage repair (DDR) gene alterations represent another potential biomarker, which has gained growing attention in several malignancies [77-80]. Since DDR alterations impair the processes of DNA damage repair, these genes lose their capability to maintain genomic stability and to contrast accumulation of spontaneous DNA damage [81-83]. In particular, a key role in these mechanisms is played by the Poly(ADP-ribose) Polymerase 1 and 2 (PARP1 and PARP2) genes, whose inhibition represents an extremely timely topic in current

medical oncology [84, 85]. On the basis of these premises, several studies have investigated the association between TMB, MSI-H, and DDR gene alterations, providing the benchmark for future trials exploring ICIs in patients harboring these aberrations [86-88]. Nonetheless, there is paucity of data regarding the role of DDR in HCC, and further efforts are needed in this direction.

In summary, the advent of genomic sequencing has the potential to provide useful information in patients with advanced disease, and analysis of next-generation sequencing data are expected to shed further light on this landscape.

Gut microbiota

The last decade has seen an impressive number of studies on gut microbiota, with part of these researches that have been selectively focused on the potential predictive value of microbiota in patients treated with ICIs [89-91]. In fact, since the gut microbiome plays a crucial role in the development and the regulation of innate and adaptive immunity, recent reports have highlighted the possible action of gut microbiome in mediating the efficacy of ICIs [92-94]. From an anatomical point of view and given the connection between liver and gut, it is readily apparent that this element could be particularly meaningful in HCC. Notably enough, gut microbiota has been suggested to promote HCC carcinogenesis in patients with liver cirrhosis, and notable interactions have been reported between immune system and microbiota, with the latter being able to modulate immunity itself [95, 96]. Similarly, and based on the action of gut microbiota on immune system, gut microbiota has been shown a role in modulating responses to immunotherapy in cancer patients. However, most of studies have been performed on melanoma and other solid tumors, with few data available in literature regarding the impact of gut microbiome in HCC patients receiving ICIs [97, 98].

Recently, a study by Zheng and colleagues reported the dynamic variation of gut microbiome during ICIs treatment in HCC by using metagenomic sequencing [99]. According to the results of this report, fecal samples from responders showed superior taxa richness and more gene counts compared to fecal samples of non-responders; thus, although these results are preliminary, gut microbiome could have an important impact on clinical responses to immunotherapy in patients with advanced HCC, with dynamic variation features of the gut microbiome suggesting early predictions of outcomes in this setting [99].

Further studies are warranted to comprehend if gut microbiome could enter into clinical practice in the next years, providing critical information for treatment decision-making and disease-monitoring. Though, given the several unanswered questions, the methodological issues and the influence of environmental and lifestyle factors, that day seems still distant so far.

Conclusions

ICIs have gradually emerged as novel therapeutic option advanced HCC. However, a non-negligible proportion of patients does not respond to immunotherapy, and an even smaller percentage achieve durable responses.

Unfortunately, no single biomarker is able to select HCC patients likely to benefit from immunotherapy, and the identification of predictors of response – not only used as single biomarkers but also in concert - is an urgent and challenging need in this setting.

Financial & competing interests' disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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CRediT authorship contribution statement

Alessandro Rizzo: Conceptualization, Methodology, Software, Data curation, Writing - original draft, Writing - review & editing. **Giovanni Brandi:** Visualization, Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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