Immunotherapy and Hepatocellular Carcinoma

Subjects: Oncology

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The combination of immune checkpoint inhibitors with target agents has been explored in hepatocellular carcinoma. The combination of an immunecheckpoint inhibitor with an anti-angiogenic drug has proved effectiveness as per the case of the IMBRAVE150 trial of atezolizumab plus bevacizumab mentioned above. Furthermore, novel immunotherapy and target agents combinations are currently being explored in first-line settings in different clinical trials to better define novel treatment opportunities for patients with HCC.

Keywords: HCC ; immune checkpoint inhibitors ; multimodal treatment ; biomarkers ; AFP

1. Introduction

Hepatocellular carcinoma (HCC) represents 90% of liver cancers and is one of the principal causes of death worldwide, with a steady rise of mortality rate [1]. Principal risk factors that might induce liver cirrhosis and are ultimately responsible for HCC disease are Hepatitis B or C viral chronic infections, alcohol abuse, obesity, diabetes, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), and certain inherited metabolic diseases [2]. HCC diverges from other solid tumors due to its origin in the context of cirrhosis. For this reason, a multidisciplinary approach with specialist figures, hepatologists, oncologists, surgeons, and radiologists, among others, is strongly required to guarantee correct patient management. HCC staging has been determined by different systems, with Barcelona Clinic Liver Cancer (BCLC) being the most common [3]. BCLC staging divides patients into stage 0 /A with very early/early disease, stage B (intermediate) with multinodular HCC, stage C for advanced HCC amenable to systemic medical treatment, and stage D for patients with terminal disease only susceptible to palliative therapies [4]. Only patients included in stage 0/ A are putative candidates for radical locoregional treatment modalities, such as surgical resection, radiofrequency ablation (RFA), and liver transplants, whereas transarterial chemoembolization (TACE) is reserved for stage B HCC [5]. Unfortunately, due to the lack of widespread screening programs that help detect the disease in early stages together with the stigma of risk factors (alcohol abuse, use of intravenous (IV) drugs) associated with the development of cirrhosis, HCC remains a silent killer. Since 2007, the mainstay of advanced HCC treatment has been limited to the use of a single drug, the oral multikinase inhibitor (MKI) sorafenib, with about three months increase in terms of survival and a series of related adverse events of importance [6]. Sorafenib is approved as a first-line strategy for patients with advanced disease, not amenable to locoregional treatments and transplant, with a Child–Pugh score of A or BCLC C criteria [7]. Recently, lenvatinib, another MKI, has received approval from the EMA and FDA and could be alternatively used in first-line settings, based on its non-inferiority activity compared to sorafenib [8]. Furthermore, in the field of targeted agents, regorafenib and cabozantinib failed to demonstrate non-inferiority to sorafenib in the first line but are approved for second-line treatment after sorafenib failure, as well as the anti-vascular endothelial growth factor receptor 2 (VEGFR2) antibody ramucirumab for patients with alpha-fetoprotein (AFP) ≥400 ng/mL [9][10][11].

In the last five years, the implementation of immunotherapy into the therapeutic armamentarium of HCC has strongly changed the medical approach to HCC patients. Therefore, immune checkpoint inhibitors (ICIs) have demonstrated promising results in Phase II and Phase III studies, and, to date, nivolumab and pembrolizumab have received accelerated approval by the Food and Drug administration (FDA) for second-line treatment of patients with advanced HCC after progression to sorafenib, while the combination of atezolizumab and bevacizumab has recently provided outstanding results in terms of overall survival (OS) and progression-free survival (PFS) in a first-line setting and has been recently approved by the FDA and European Medicines Agency (EMA) [12][13][14]. It is worth noting that several studies are currently investigating the combination of ICIs with different drugs, including targeted agents and chemotherapy, and novel immunotherapy strategies beyond ICIs are in current development. We herein provide an overview of the immune landscape of HCC, discuss the results of principal clinical trials that have led to currently approved immunotherapies and investigate potential immune biomarkers of response to improve outcomes in a disease that has always needed efficacious treatments.

2. Immune Landscape of Hepatocarcinoma Disease

The liver has a peculiar anatomy and fulfills functions including uptake of arterial and portal blood, filtration of gut pathogens, and excretion of toxic waste materials, a feature that leads to exposure to a high load of antigens [15]. This hepatic reticulo–endothelial system that comprises sinusoids, Kuppfer cells, and liver endothelial sinusoidal cells (LESC) activates innate T-cells through antigen presentation, causing a tolerogenic immune response in a physiological status [16]. It has been reported in several studies how the immune surveillance system could be damaged in the context of cirrhosis. This continuous inflamed status of the liver leads to the recruitment of cytokines and immune components, ultimate actors in neoplastic dysregulation in which HBV and HCV viruses could contribute to carcinogenesis development [17]. Immune tolerance that characterizes the evolution of HCC is regulated by innate and adaptive immune cells present in the immune tumor microenvironment (TME) such as CD4+ and CD8+ T-cells, dendritic cells (DCs), natural killer (NK) cells, myeloid-derived suppressor cells (MDSC), tumor-associated macrophages (TAMs) that express and up-regulate immune checkpoints on their surface as programmed cell death protein 1 (PD-1) and the cytotoxic lymphocyte protein 4 (CTLA-4) [18]. PD-1 is responsible for T-cell exhaustion and prevents T-cell activation by releasing cytotoxic mediators, and CTLA-4 impedes activation of T-cells by replacing CD28 in the interaction with CD80/86 ligands on antigen-presenting cells (APC) [19].

All these components of TME act with intricate processes as decreased tumor-associated antigen (TTA) recognition, accumulation of immune suppressive cells, and interaction between immune checkpoints and their ligands, leading to a final balanced immunotolerant status [20]. Moreover, the immunotolerance of liver cancer is accompanied by the release of several cytokines and regulatory factors, such as transforming growth factor (TGF)-β, which acts as an immunosuppressive factor [21].

3. Clinical Evidence of Immune Checkpoint Inhibitors in Hepatocarcinoma

By contrast, the phase III randomized CheckMate 459 trial (NCT02576509) which explored the efficacy and safety of nivolumab treatment in first-line treatment compared with sorafenib standard treatment did not show a statistically significant improvement in the primary endpoint of the overall survival (OS) (16.4 months versus 14.7 months in the nivolumab and sorafenib arm, respectively, Hazard Ratio (HR): 0.85; Confidence Interval (CI) 0.72–1.02; p = 0.0752), and in median progression-free survival (mPFS) (3.7 months vs. 3.8 months). However, RR was significantly higher in the experimental arm (15%) compared to 7% in the sorafenib control arm [22]. Although nivolumab treatment showed a clinical benefit in all the preplanned patient subgroups, with a favorable toxicity profile, the study did not change the standard of treatment for patients with naïve advanced HCC.

The anti-Programmed Death-Ligand 1 (PD-L1) antibody atezolizumab was explored in a first-line setting in the Phase Ib GO30140 trial (NCT02715531) alone or in combination with the anti-VEGF monoclonal antibody bevacizumab. Arm A of the trial evaluated the combination of atezolizumab and bevacizumab every three weeks whereas Arm F randomized patients 1:1 to receive atezolizumab plus bevacizumab or atezolizumab as a single agent. The primary endpoint of Arm A, RR, was 36%, while PFS, the primary endpoint of Arm F, was 5.6 months with the combination and 3.4 months with atezolizumab single agent (HR: 0.55; 80% CI 0.4–0.74; p = 0.0108). Regarding safety profile, which was another co-primary endpoint of the study, a higher rate (68%) of treatment-related adverse events (TRAEs) was reported in atezolizumab plus bevacizumab combination versus 41% in the atezolizumab single-agent arm [23]. Subsequently, the Phase III Imbrave150 trial randomized 2:1 501 patients to receive a combination of atezolizumab plus bevacizumab or sorafenib as first-line treatment, respectively. The primary endpoints of the study were OS and PFS as per the independent review facility (IRF) assessed-response evaluation criteria in solid tumors (RECIST) 1.1.

Therefore, median OS was not reached in the atezolizumab plus bevacizumab combination that resulted in 13.2 months in the sorafenib group (HR: 0.58; 95% CI 0.42–0.79; p = 0.0006). OS rates were 84.8% and 67.2% with the experimental combination and the sorafenib arm obtained 72.2% and 54.6% at 6 and 12 months, respectively (HR: 0.58; 95% CI 0.42–0.79; p = 0.0006). Median PFS was 6.8 months in the combination arm and 4.3 in the sorafenib arm (HR: 0.59; 95% CI 0.47–0.76; p < 0.0001). The RR was 28% in the experimental arm versus 12% with control (95% CI 23–33 vs. 7–17, respectively, p < 0.0001), but reached 33% versus 13% (95% CI 28–39 vs. 95% CI 8–19; p < 0.0001) when evaluated per modified RECIST (mRECIST) criteria. Toxicities reported were more frequent with the experimental combination, with hypertension the most common grade 3–4 TRAE [14]. These data changed clinical practice with breakthrough approval of atezolizumab plus bevacizumab combination by the FDA and EMA as first-line treatment of patients with unresectable or metastatic HCC who had not received systemic therapy. In the same way, the updated OS analysis conducted with 12 months of additional follow-up from primary analysis confirmed the strong efficacy of atezolizumab + bevacizumab

combination over sorafenib treatment, with median overall survival of 19.2 months for the combination versus 13.4 months for sorafenib. Moreover, updated results of RR were consistent with the ones from the primary analysis (29.8% per RECIST 1.1) with a higher rate of complete response (7.7%) than previously reported [24].

The efficacy and safety findings coming from the combination arm with tremelimumab at 300 mg have opened an avenue to the ongoing Phase III HIMALAYA trial (NCT03298451) of tremelimumab + durvalumab treatment compared to sorafenib in a first-line setting, where results are strongly awaited, as the two drugs were already granted orphan drug designation by the FDA in January 2020 [25].

4. Combining Immune Checkpoint Inhibitors with Targeted Agents

The development of HCC structure from dysplasia is a process influenced by proangiogenic factors such as angiopoietins, VEGF, transforming growth factors, basic fibroblast growth factors (bFGF), and platelet-derived growth factor (PDGF) that are secreted by TME and enhance tumor blood requirement from arteries to guarantee growth and metastatic spread. By contrast, tumor vessels are structurally imperfect and with a network of sinusoids that differ from hepatic sinusoids of a normal liver because they are more “capillarized” for the presence of a basement membrane and lack of fenestration [26]. Based on that, anti-VEGF strategies have represented a mainstay in HCC treatment for many years.

Since then, treatment with other MKI molecules regorafenib and cabozantinib has been explored, without achieving statistically significant benefit in first-line treatment but in second-line treatment in the RESORCE (NCT01774344) and CELESTIAL (NCT01908426) Phase III trials, respectively. Interestingly, regorafenib treatment provided a median OS of 10.6 months, while the median OS of the sequence represented by sorafenib in first-line treatment and regorafenib in second-line treatment was 26.0 months, compared to 19.2 months with sorafenib and then placebo [9]. On the other hand, in the CELESTIAL trial, cabozantinib treatment in second or subsequent lines provided 10.2 months OS compared to 8 months with placebo (HR: 0.76; 95% CI 0.63–0.92; $p = 0.005$) and 5.2 months median PFS with cabozantinib and 1.9 months with placebo (HR: 0.44; 95% CI, 0.36–0.52; $p < 0.001$) [10].

Importantly, the tumor vessel-altered phenotype not only contributes to the new angiogenesis process that nourishes liver tumor but also determines a down-regulation of immune TME effectors such as CD8+ T-cells and a final immunosuppressive microenvironment in which T regs, MDSCs, and M2 polarized TAMs release immunosuppressive cytokines and finally block T-cells, NK cells, and DCs activation [27].

Based on this strong rationale, the combination of immune checkpoint inhibitors with anti-angiogenic drugs was examined in HCC and has proved effective strategies as per the case of the IMBRAVE150 trial of atezolizumab plus bevacizumab mentioned above. Furthermore, sintilimab plus anti-VEGF monoclonal antibody IBI305 safety and efficacy is currently being explored in first-line settings in the ongoing Phase II/III ORIENT-32 trial (NCT03794440). The same combination approach has been tried in second-line treatment with the anti-VEGFR-2 ramucirumab plus anti-PD-L1 durvalumab in the HCC cohort of the NCT02572687 Phase Ib trial. RR was 11% in the entire cohort but increased to 18% in the PD-L1 positive selected population, with a globally safe profile, suggesting future possible larger investigations in this setting [28].

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