HCC and Molecular Targeting Therapies

Subjects: Allergy

Contributor: Ferdinando Carlo Sasso

Hepatocellular carcinoma (HCC) is one of the leading causes of death from cancer in the world. Recently, the effectiveness of new antiviral therapies and the HBV vaccine have reduced HCC's incidence, while non-alcoholic steato-hepatitis is an emerging risk factor. This entry focuses on antiangiogenic molecules and immune checkpoint inhibitors approved for HCC treatment and possible future approaches.

Keywords: liver ; HCC ; drugs ; trials

1. Introduction

The most frequent liver cancer, and seventh by type of cancer in the world, is hepatocellular carcinoma (HCC), which is commonly associated with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections that usually develop during the cirrhosis stage [1][2][3][4]. HBV integrates into the genome and has a recognized carcinogenic action, while HCV does not integrate into the genome, but can induce epigenetic changes that can disregulate oncogenes [5][6]. Vaccination for HBV and new antiviral therapies that limit or clear the viral load reduce the risk of HCC and all hepatic and extrahepatic viral complications [5][7]. However, special conditions persist that require the monitoring of these patients [7][8][9][10]. In fact, the eradication of HCV with direct-acting antivirals (DAAs) does not delete the HCC risk and the histological picture of cirrhosis and the possible interference of the DAA with the genome can maintain a residual risk [6]. The presence of occult HBV can also represent a potential carcinogenic stimulus [11]. In addition to viruses, alcohol abuse, metabolic liver disease, and obesity represent other important risk factors for HCC. While in a condition of alcohol abuse the pathophysiological evolution from alcoholic cirrhosis to the development of HCC is well understood, the relation between a dysmetabolic condition and HCC appears to be much more complex. Non-alcoholic fatty liver disease (NAFLD) currently represents the most frequent manifestation of chronic liver disease [12]. The development of non-alcoholic steato-hepatitis (NASH) is an element of possible progression to cirrhosis with an increased risk of HCC [13][14]. Host genetic variants, especially the gene coding for patatin-like phospholipase domain-containing 3 (PNPLA3), may play a role in the development of HCC independently of activity and the extent of liver damage [15]. Two important elements may delay the diagnosis of HCC: many cases of HCC develop in patients with NAFLD in the absence of cirrhosis; and, secondly, people do not consider NAFLD to be as dangerous as viral liver infections [16]. Recently, the link between metabolic syndrome and liver diseases has been highlighted even more with the definition of metabolic-associated liver diseases (MALDs) [17]. Insulin resistance seems to be the connecting element between the diseases and underlies the development of type 2 diabetes (T2D) [18][19]. This latter is burdened with numerous complications and is associated with an increased risk of HCC in patients with NASH cirrhosis [20][21][22][23][24][25][26]. Transcription factors such as Kruppel-like factor 6, abnormal methylation, and immune dysregulation might help to explain the dysregulation of nine hub genes that have been identified as possible links between these two diseases [27].

The diagnosis of HCC is generally made through standard ultrasound with a contrast medium, which in the surveillance phase allows for early detection of small lesions [28]. Transient elastography using fibroscan represents a support method capable of monitoring some populations at greatest risk of HCC [29]. The diagnosis of HCC is confirmed with second-level methods and a histological biopsy that represents the gold standard [29][30].

The therapeutic strategies of HCC are limited by the patient's basal clinical conditions. The coexistence of cirrhosis is an important limitation already burdened by complications such as portal hypertension and liver failure [31][32]. Whenever possible, selective surgical resection is the ideal method for eradicating the disease with a good expectation in terms of survival [33]. Alternatively, loco-regional treatments, such as radiofrequency, microwave, laser, and trans-arterial chemoembolization (TACE) treatments, allow us to obtain good results in terms of efficacy with limited damage for the most fragile patients. Liver transplantation can be considered in younger patients in order to obtain a synergistic action on HCC and the underlying disease, especially under particular conditions represented by an early stage of disease and favorable cancer biology, which offers excellent survival expectations [34][35][36][37]. However, constant monitoring of the patient and adherence to immunosuppressive therapy remain essential [38][39].

The failure or inability to carry out interventional eradication therapies orientates the therapeutic strategy to the use of drugs.

2. Drugs Approved for HCC

Several new substances have changed the field of treatment for patients with HCC. Initially, no effective therapy was available after the failure of loco-regional approaches; however, in 2007 a new age started with the approval of sorafenib as the first effective systemic agent in patients with advanced HCC (aHCC). However, it took nearly 10 years for new and effective drugs to be used in both first-line and subsequent treatment. Since their recent approval, these new substances have changed the field of palliative treatment strategies for patients with aHCC, and their sequential application has been shown to be able to significantly prolong patient survival in the palliative approach. Recently, molecular targeted therapy has emerged as a new strategy of cancer treatment and, compared with traditional therapies, operates more specifically by destroying cancer cells, reducing damage to normal tissues, and being safer and better tolerated by patients [40][41]. Several studies detected dozens of mutations and driver genes with high frequency that could be considered to be the origin of HCC. Altered CTNNB1 is commonly found in HCC (23–36%) and is linked to WNT-β-catenin signaling. Active CTNNB1 mutations are more common in hepatitis C virus (HCV)-related HCC (more than half of HCV patients) than in hepatitis B virus (HBV)-related HCC and are associated with a particular WNT gene expression profile [42]. VEGFA is another driver gene in HCC (frequency: 7–10%) and mostly detected as copy number alterations [41]. Furthermore, a high level of VEGFA in HCC cells could lead to excessive production of hepatocyte growth factor (HGF), which induces tumor cell proliferation. KRAS (rat sarcoma of Kirsten), an isoform of RAS, is an oncogene that is frequently mutated in most cancers, although the mutation rate in HCC is relatively low (about 1%) [43]. Given the variety of mutations identified in a given patient, it is unlikely to have a therapeutic agent that effectively targets the majority of HCCs, thus requiring a combination of treatments to target different mutations [44]. Targeted molecular therapy acts on overexpressed cell receptors, key genes, and certain tumor cell marker molecules by selecting specific blockers to inhibit tumor growth, progress, and metastasis [40][45]. It is well known that, at any stage of HCC, vascular endothelial cell proliferation is active and the expression of VEGFR molecules on the cell surface is significantly upregulated [46]. Angiogenesis in cancer tissues has a major impact on the biological invasion capabilities of the cancer [47]. Therefore, blocking VEGF/VEGFR and reducing angiogenesis in tissues are considered to be new ideas for targeted therapy in HCC. Many molecularly targeted drugs have, both commercially and investigationally, achieved significant results. To date, based on phase III studies, six systemic therapies have been approved (atezolizumab plus bevacizumab, sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab) and three additional therapies have received accelerated Food and Drug Administration (FDA) approval due to evidence of efficacy. These drugs target the VEGFR-2 signal at various levels together with other receptors involved in the angiogenic process, with the exception of ramucirumab, which selectively targets VEGFR-2, so all these agents could be synergistically associated with immune checkpoint inhibitors [48]. Moreover, new studies are exploring drug combinations, including checkpoint inhibitors and tyrosine kinase inhibitors or anti-VEGF drugs, and even combinations of two immunotherapy regimens.

3. Combined Therapies

Based on the activity of single-agent immune checkpoint inhibitors (ICIs) and on a better understanding of the tumor immunosuppressive microenvironment (TME), several combination strategies can be considered and many of them have already entered into clinical development. The FDA, EMA, and other regulatory agencies worldwide have approved the atezolizumab plus bevacizumab combination for first-line therapy in HCC. This combination will therefore set a new standard of care for treatment-naive patients. Combinations result in a consistent twofold increase in response rates, with about 5% of patients in complete remission and long survival times of more than 18 months. In parallel, additional toxicities from combinations increase the number of serious adverse events leading to treatment discontinuation. ICIs have shown promising activity when paired with anti-angiogenic agents, other molecularly targeted therapies, and complementary ICIs. The VEGF pathway promotes local immune suppression through the inhibition of antigen-presenting cells and effector cells as well as through the activation of suppressive elements, including Treg cells, myeloid-derived suppressor cells, and tumor-associated macrophages, providing the rationale for combining ICIs with anti-angiogenic agents [49].

A phase Ib trial of the combination of lenvatinib and pembrolizumab as a first-line therapy in 100 unresectable patients with HCC demonstrated durable PFS [50]. Based upon the unique immunomodulatory and antiangiogenic profile of cabozantinib, another phase III trial to determine the efficacy of the combination of cabozantinib and atezolizumab compared with sorafenib or cabozantinib alone is ongoing [51][52].

From preliminary findings with the combination of ipilimumab and nivolumab, the best median mOS (22.8 months) was obtained with the highest dose (3 mg/kg once every 6 weeks) of the former and a lower dose of the latter (1 mg/kg once every 2 weeks) [53]. Such encouraging results have led to accelerated approval of this combination by the FDA to treat patients with HCC after sorafenib.

A similar effect was observed with the combination of a single 300 mg dose of tremelimumab combined with a continuous dose of the PDL1 inhibitor durvalumab. Tremelimumab is a fully human monoclonal antibody that binds to the CTLA-4 molecule. CTLA4 is expressed on the surface of activated T lymphocytes and, by binding to CTLA4, tremelimumab mediates downregulation of T-cell activation and then the immunitary response. Durvalumab is an IgG1 monoclonal antibody that binds with high affinity to the PD-L1 receptor and shows the same mechanism of action as atezolimumab. Interestingly, this single, high priming dose of tremelimumab resulted in an early burst of proliferating CD8+ T cells in peripheral blood [54]. These findings are in line with observations in melanoma, indicating that the activity of CTLA4 inhibitors is dose-dependent and that the first doses of CTLA4 inhibitors cause a proliferative burst of CD4+ and CD8+ T cells, probably related to the increased efficacy of the combination [55][56]. In HCC, as for other cancer types, combination regimens increase the rate of treatment-related adverse events (TRAEs) that are nevertheless tolerable.

In patients with unresectable HCC, a phase Ib study showed that lenvatinib plus pembrolizumab has promising anti-tumor activity; the mOS was 22 months and toxicities were manageable, with no unexpected safety signals [50].

An important question in the evaluation of the efficacy of a combination regimen is to understand whether improvements in time-to-event medians and objective response rates are due to synergy and not because of the independent additive effects of two active agents, which can also be achieved by a sequential approach [57]. In the absence of head-to-head trials or established biomarkers to guide the choice of therapy, treatment decisions must rely upon the magnitude of benefits, the toxicity profile, and drug availability. Biomarker data to help decision-making and to guide treatment for advanced stages of HCC are limited. An elevated level of serum α-fetoprotein is an established biomarker of poor prognosis across all stages of HCC and is associated with tumor VEGF pathway activation [58]. Serum levels of α-fetoprotein became the first biomarker predictive of response, with the finding of a survival benefit of ramucirumab over a placebo only in patients with α-fetoprotein levels ≥400 ng/mL [59]. Thus, ramucirumab is only indicated when α-fetoprotein levels are beyond this cut-off value. However, unlike ramucirumab, the treatment benefits from multi-kinase inhibitors, including sorafenib, lenvatinib, regorafenib, and cabozantinib, occur across a range of baseline α-fetoprotein values, likely owing to a broader spectrum of target inhibition on patients with elevated α-fetoprotein levels at baseline. Changes in α-fetoprotein levels on treatment were shown to correlate with clinical outcomes on systemic therapy, with declining α-fetoprotein levels linked to prolonged PFS and overall survival and increasing α-fetoprotein levels associated with tumor progression [60]. A variety of biomarkers that benefit from immune-checkpoint inhibition are under investigation across different solid tumors, including HCC. A meta-analysis of outcomes from >3500 patients showed that tumor PDL1 expression is associated with a worse prognosis in HCC, including a poorly differentiated histology, high levels of α-fetoprotein, and shorter overall survival [61]. The tumor lymphocytic infiltration immune class gene signature and CTNNB1 mutation status in subsets of HCC tumors also warrant examination for predictive value in patients treated with ICIs [62][63][64]. Unfortunately, no single biomarker was able to select HCC patients likely to benefit from immunotherapy, and the identification of predictors of response is an urgent and challenging need in this setting.

It would be very interesting, especially in the case of HCC post NAFLD, to evaluate the mechanistic assumptions and the possible clinical indication of the association of standard therapy with metformin, which in several other neoplastic conditions has shown an effect of enhancing therapies, especially in the second-line treatment [65]. The main characteristics of the above trials are reported in **Table 1**.

Table 1. FDA-approved drugs and ongoing trials for HCC.

Drugs	Targets	Study	Primary Endpoint
Nivolumab + Ipilimumab	**Anti-PD1 + Anti-CTL4**	**CHECKMATE 040 (ongoing multi-center, multiple parallel cohort, open-label clinical trial) [53]**	**ORR**
Camrelizumab + Apatinib	**Anti-PD1 + VEGFR-2 tyrosine kinase inhibitor**	**RESCUE (nonrandomized, open-label, Phase II trial) [66]**	**ORR**
Pembrolizumab	**Anti-PD1**	**KEYNOTE 240 (randomized, double-blind, Phase III trial) [67]**	**OS and PFS**

Drugs	Targets	Study	Primary Endpoint
Tislelizumab vs. Sorafenib	Anti-PD1 + Multi-kinase inhibitor	RATIONALE 301 (global, Phase III, randomized, open-label, multi-center study) [68]	OS between two treatment groups

VEGFR, vascular endothelial growth factor receptor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; +, in combination with; vs, compared with.

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