We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 9

Biologic and Immunotherapy Developments in Advanced Hepatocellular Carcinoma

Mohammad Telfah, Mohammed Al-Jumayli and Anwaar Saeed

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79872

Abstract

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, and the second leading cause of cancer-related mortality worldwide with a very poor 5-year survival. Treatment for HCC includes surgery, liver-directed therapies and systemic therapies. Until 2008, no effective systemic therapy was available for advanced HCC. Sorafenib is the first drug to show improvement in overall survival among patients with advanced HCC in comparison to placebo, and it is approved by U.S. Food and Drug Administration (FDA) as a first-line treatment of advanced HCC. After sorafenib approval, several targeted and immune therapies were tested and showed efficacy in advanced HCC. Lenvatinib has been shown to be non-inferior to sorafenib as first-line treatment. Both nivolumab and regorafenib showed improvement in overall survival among patients with advanced HCC as a second line treatment after progression on sorafenib, and both are FDA approved for this indication. There is a limited role for cytotoxic agents in the treatment of advanced HCC.

Keywords: hepatocellular, carcinoma, HCC, kinase, inhibitors, TKI, VEGFR, sorafenib, lenvatinib, regorafenib, immunotherapy, PD-L1, nivolumab

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver. HCC is the second leading cause of cancer-related mortality worldwide with a very poor 5-year survival. The incidence of HCC has been increasing over the past decades [1]. Risk factors for HCC include hepatitis B and C infection, alcohol use, non-alcoholic steatohepatitis, and aflatoxin.

Treatment approaches for HCC depend on the stage and the hepatic function, and includes surgical therapies (liver transplantation, resection, and ablation) and nonsurgical therapies, which may be liver-directed (percutaneous ethanol injection, radiofrequency ablation, transarterial embolization, external beam radiation therapy) or systemic therapies.

Until 2008, there was no effective systemic therapy for advanced HCC. Cytotoxic chemotherapy has not been used routinely as of low efficacy and poor functional status for patients with advanced HCC, who often have cirrhosis. Since the advent of sorafenib in 2008, there has been a surge of several targeted and immune therapies with various degree of effectiveness. In this chapter, systemic therapies for advanced HCC will be reviewed. Those include oral kinase inhibitors, antiangiogenic monoclonal antibodies, immune-therapeutic approaches and cytotoxic chemotherapies.

2. Kinase inhibitors

2.1. Sorafenib

Sorafenib is a multi-kinase inhibitor of vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptor (PDGFR) and Raf family kinases [2]. Sorafenib has shown to improve overall survival in comparison to placebo in advanced HCC, and it was the first drug to get Food and Drug Administration (FDA) approval as a first-line treatment for Child-Pugh score-A HCC. In the multicenter European SHARP trial, 602 inoperable HCC and Child-Turcotte-Pugh-A cirrhosis patients, were assigned to sorafenib (400 mg twice daily) or placebo [3]. The primary endpoint of the trial was overall survival, which was significantly longer in the sorafenib-treated group (10.7 vs. 7.9 months). Time to radiologic progression was also longer (5.5 vs. 2.8 months). Objective response rates were low at 2%.

Sorafenib was well tolerated in this trial. Diarrhea and hand-foot skin reaction were the only grade 3 or 4 adverse effects that occurred significantly more often in the treated group; (8 vs. 2%) and (8 vs. <1%) respectively. There were no differences in liver dysfunction or bleeding.

An exploratory analysis of SHARP trial showed that hepatitis C related HCC has the highest median overall survival advantage of 6.6 months (14 vs. 7.4 months). This is in comparison to 3.6 months (9.7 vs. 6.1 months) in those with HBV related cirrhosis and 2.3 months (10.3 vs. 8 months) in those with alcohol-related liver disease [4].

Hepatitis B virus is more prevalent in the Asian patients than in the Western population. Sorafenib was tested as a first-line treatment in Asian patients in a placebo-controlled phase III trial in which 226 patients with Child-Turcotte-Pugh A cirrhosis received sorafenib 400 mg twice daily or placebo [5]. Patients receiving sorafenib had significantly higher median overall survival (6.5 vs. 4.2 months). Grade 3 or 4 side effects were similar to SHARP trial.

Based on the results of SHARP trial, the FDA approved sorafenib monotherapy as first-line therapy for unresectable HCC.

It is worth mentioning that the patients enrolled in the above trials had mostly Child-Turcotte-Pugh A cirrhosis. This is not representative of the real practice where a significant number of

patients have more advanced cirrhosis. FDA approval of sorafenib for HCC did not particularly specify the underlying cirrhosis state. Data regarding safety and efficacy of sorafenib in patients with Child-Turcotte-Pugh B or C cirrhosis are limited, and suggest that patients have poorer overall survival and overall worse side effect profile in comparison to patients with Child-Turcotte-Pugh A. Advanced progressive cirrhosis rather than sorafenib itself might be an explanation for such differences [6, 7].

Sorafenib is associated with several side effects such as hypertension, cardiotoxicity, arterial thromboembolism, bleeding, renal toxicity, hand-foot skin reaction and others. Sorafenib has been associated with potentially fatal liver toxicity. Liver function tests should regularly be monitored during treatment.

2.1.1. Combining sorafenib with doxorubicin

In a phase II trial, the combination of six cycles of doxorubicin with sorafenib 400 mg twice daily was compared to sorafenib and placebo [8]. Combination therapy was associated significantly longer median time to tumor progression (6.4 vs. 2.8 months) and median overall survival duration (13.7 vs. 6.5 months). The side effect profile was not significantly worse with combined therapy. However those results were not reproduced in the randomized phase III trial, Cancer and Leukemia Group B [CALGB] trial 80,802 [9]. The study was stopped early by the data monitoring safety board after a planned interim analysis suggested futility for the combination. In a preliminary report presented at the 2016 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, median overall survival was not significantly better for the combination (9.3 vs. 10.5 months), nor was median progression-free survival (3.6 vs. 3.2 months), but toxicity was worse.

2.2. Lenvatinib

Lenvatinib is a multi-kinase inhibitor of VEGFRs, fibroblast growth factor receptors (FGFR), (PDGFR), c-Kit, and the RET proto-oncogene [10].

A randomized noninferiority trial, the REFLECT study, compared lenvatinib (12 mg once daily for body weight ≥60 kg, 8 mg daily for <60 kg) with sorafenib (400 mg daily for all patients) in 954 patients with unresectable HCC and no prior systemic therapy (99% Child-Turcotte-Pugh A) [11]. The predefined noninferiority margin (primary endpoint overall survival) was 1.08. Lenvatinib was noninferior to sorafenib (median overall survival 13.6 vs. 12.3 months, hazard ratio 0.92, 95% CI 0.79–1.06), the objective response rate was higher (24 vs. 9%), and median time to progression was longer (7.4 vs. 3.7 months, hazard ratio 0.66, 95% CI 0.57–0.77). Lenvatinib leads to higher grade 3 or 4 hypertension (23 vs. 14%), while sorafenib was associated with higher hand-foot skin reaction (11 vs. 3%).

Lenvatinib was approved in Japan in March 2018 for unresectable HCC. Lenvatinib is not approved by FDA yet.

Both sorafenib and lenvatinib can be used in the first-line treatment of advanced HCC. There are no data on second-line treatment after lenvatinib and whether lenvatinib is effective as a second line after sorafenib.

2.3. Regorafenib

Regorafenib is an antiangiogenic (including VEGFR-1, VEGFR-2, and VEGFR-3), anti-stromal, and an oncogenic tyrosine kinase inhibitor that is structurally similar to sorafenib [12].

In the randomized RESORCE trial, 573 patients who received sorafenib for at least 20 days at a dose of at least 400 mg daily and who had radiologic progression were randomly assigned to regorafenib (160 mg once daily for 3 weeks on and 1 week off) or placebo [13]. Regorafenib was associated with significantly higher median OS (10.6 vs. 7.8 months, hazard ratio for death 0.63) and disease control (objective response plus stable disease; 65 vs. 36%).

Treatment was relatively well tolerated; grade 3 or 4 hypertension, hand-foot skin disease and fatigue were more frequent with regorafenib. Sixty-eight percent of patients treated with regorafenib required dose modification for adverse events compared with 31% of the placebo group.

In April 2017, the FDA expanded the indications for regorafenib to include patients with HCC who had been previously treated with sorafenib.

Regorafenib is an alternative to nivolumab for second-line HCC treatment. There are no trials comparing regorafenib with nivolumab in this setting.

2.4. Cabozantinib

Cabozantinib is another inhibitor of several receptor tyrosine kinases, including the hepatocyte growth factor/c-MET and VEGFR [14]. Efficacy in patients with previously treated advanced HCC was shown in the placebo-controlled phase III CELESTIAL trial [15]. In a preliminary report, in the group of patients receiving second- or third-line treatment, median overall survival was significantly better with cabozantinib (10.2 vs. 8.0 months), and the difference was more pronounced when the analysis was limited to patients whose only prior therapy was sorafenib (median overall survival 11.3 vs. 7.2 months). The most common grade 3 or 4 adverse events with cabozantinib were palmar-plantar erythrodysesthesia (17 vs. 0 in the placebo group), hypertension (16 vs. 0%), increased aspartate aminotransferase (12 vs. 7%), fatigue (10 vs. 4%), and diarrhea (10 vs. 2%).

2.5. Axitinib

Axitinib is a selective kinase inhibitor that inhibits VEGFR. Axitinib was not superior to best supportive care alone in a randomized phase II trial comparing best supportive care plus axitinib (starting dose 5 mg twice daily) with placebo in 202 patients with advanced HCC who progressed on or were intolerant of one prior antiangiogenic therapy [16]. The difference in median overall survival (the primary endpoint), was not statistically significant (12.7 vs. 9.7).

2.6. Sunitinib

Sunitinib is another orally active multi-kinase inhibitor that targets a variety of tyrosine kinases in addition to VEGFR, including PDGFRs, KIT, RET, and FMS-like tyrosine kinase 3 (FLT3) [17].

http://dx.doi.org/10.5772/intechopen.79872

Sunitinib was significantly inferior to sorafenib in a phase III trial that directly compared both drugs in 1073 previously untreated patients with advanced HCC [18]. The trial was closed prematurely when an interim analysis revealed that patients receiving sunitinib had significantly worse survival (median 7.9 vs. 10.2 months) and more frequent and severe treatment-related toxicity.

3. Antiangiogenic monoclonal antibodies

3.1. Bevacizumab

Bevacizumab is a monoclonal antibody directed against VEGFR that has some activity in advanced HCC. Efficacy was shown in a trial in which 46 patients with advanced nonmetastatic HCC received single-agent bevacizumab at a dose of either 5 or 10 mg/kg once every other week [19]. An objective response was documented in six (13%, one complete), and the median progression-free survival was 6.9 months. The most common grade 3 or 4 toxicities were hypertension (15%), thrombosis (6%), and major bleeding (11%).

Bevacizumab is also active in combination with capecitabine, with or without oxaliplatin [20, 21], and gemcitabine combined with oxaliplatin (GEMOX) [22]. Whether any of those combination regimens are better than bevacizumab alone is not clear and will require randomized trials.

3.2. Ramucirumab

Ramucirumab is a recombinant monoclonal antibody that binds to VEGFR-2. The REACH trial failed to show a significant survival advantage relative to placebo (median overall survival 9.2 vs. 7.6 months) in patients with advanced HCC who progressed on sorafenib [23]. An unplanned group analysis suggested a possible survival benefit in patients with a high initial level of alpha-fetoprotein (AFP) above 400 ng/mL) at diagnosis. A follow-up phase III trial in patients with AFP-elevated HCC is ongoing.

4. Immunotherapeutic approaches

4.1. Introduction

Immune-based approaches that focus on vaccination strategies, cytokines or non-specific T cell activation have been tested for many years in HCC without promising result. However, the recent advancement in immune-oncology with the FDA approval of many immune checkpoint inhibitors, sparked a great interest in the immune-based treatment approaches for patients with HCC. The strategy of adopting an immunocentric approach to HCC treatment may be potentially more efficacious and less toxic. Interestingly, what makes the immunotherapy appealing in liver cancer is that HCC is a high immunogenic cancer, due to high blood flow with unique vast tumor antigen repertoire because of mutations and aberrant expression profiles [24]. On the other hand, there is an inherently immunosuppressive microenvironment

of the liver; "Tolerogenic Liver"; that helps evade the immune response. The liver's pathway to immune tolerance is multifactorial. T-cells are stimulated through a dual signaling pathway that requires the interaction of T cell receptors (TCR) with major histocompatibility complex (MHC)/peptide complexes on antigen presenting cells (APCs) and expression of co-stimulatory molecules on T cells and APCs. Down-regulation of MHC class I molecules on tumor cells induces impairment of tumor antigen processing and presentation [25]. In addition, a reduced expression of co-stimulatory molecules, such as B7-1 and B7-2, in HCC leads to T cell anergy [26]. Programmed cell death protein-1 (PD-1) overexpression in tumors promotes immune evasion and tumor growth by suppressing T-cell response [27]. PD-L1 is not the only immunosuppressive factor in the tumor microenvironment. HCC immune evasion can also be achieved through overexpression of MHC class II molecules in tumor cells, which leads to $CD4^+$ T cell anergy in the absence of co-stimulatory molecules (CMs) on T cells and APCs. A better understanding of the antigenic profile of HCC and tumor microenvironment has helped to develop a refined immunotherapeutic strategies in treatment of HCC [28].

4.2. Indirect immunological strategies

4.2.1. Checkpoint inhibitors

Checkpoint Inhibitors play critical roles in cancer immunology. Blockading the PD-1/PD-L1 pathway could modulate the tumor microenvironment, reactive T-cell and prime the endogenous antitumor immune responses. Treatment with checkpoints inhibitors have shown benefits in clinical trials of HCC. Common immune checkpoint proteins include cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), PD-1, programmed cell death ligand one (PD-L1), lymphocyte activation gene three protein (LAG-3), B and T lymphocyte attenuator (BTLA), T-cell immunoglobulin and mucin-domain-containing (TIM-3), VISTA and OX40 [29, 30].

4.2.1.1. CTLA-4 inhibitors

CTLA-4 is constitutively expressed in activated T cells and NK cells [31]. CTLA-4 inhibitors prevent the binding of CTLA-4 to B7-1 and B7-2, thereby actively encourage the activation of T cells. CTLA-4 was the first checkpoint studied in HCC. Tremelimumab, an anti-CTLA-4 monoclonal antibody, was tested in a phase II study in a 21 patients with advanced HCC and hepatitis C. The disease control rate was (76.4%), median OS and PFS were 7.5 and 6.4 months respectively. Moreover, viral loads of HCC were significantly reduced. Although a short-lived remarkable rise in serum transaminases was observed after the first dose, no patients experienced immune-related adverse events or serious hepatotoxicity [32]. In another non-comparative clinical trial involving patients with advanced HCC, a combination therapy of tremelimumab and radiofrequency ablation increased the number of intratumoral $CD8^+$ T cells and reduced HCV viral loads [33].

4.2.1.2. PD-1 inhibitors

The PD-L1/PD-1 pathway is another mechanism of tumor-induced immune tolerance. PD-1 expression on effecter phase $CD8^+$ T cells is increased in patients with HCC compared to

no HCC cirrhotic patients [34]. Moreover, there is frequent and early disease progression in patients with HCC with higher numbers of tumor-infiltrating and circulating PD-1 + $CD8^+$ T cells post hepatic resection [35]. Therefore, a supporting great rationale exists for using PD-1 and PD-L-1 blocking antibodies against HCC. Some PD-1 inhibitors, such as nivolumab, pembrolizumab, and pidilizumab, have been investigated for cancer treatment.

The CheckMate-040 phase I/II trial studied the safety and antitumor effect of nivolumab in 48 patients with advanced HCC [36]. The target population included patients with intermediate or advanced HCC and preserved liver function (Child-Turcotte-Pugh-A cirrhosis) who were candidates for systemic therapy and had progressed or were intolerant to sorafenib. In the escalation and expansion cohorts, objective tumor responses occurred in 15 and 20% of patients, respectively. There were durable responses that lasted for a median of 17 months. An additional 45% of patients had a stable disease associated with durability, lasting 6 months at minimum. Those responses were consistent across the different HCC risks, and both in sorafenib-naïve and sorafenib-exposed patients.

Overall, frequencies of grade 3/4 treatment-related AEs were 20%. Only 3% of patients discontinued nivolumab because of treatment-related adverse events, while no treatment-related deaths occurred. Elevated transaminases was the most frequent laboratory alteration (20%). However, only 5% of the patients had grade 3 or higher. Immune-related hepatitis requiring steroid therapy. CheckMate-040 showed that nivolumab might be effective with acceptable toxicity in HCC, regardless of hepatitis status. On September 22, 2017, and based on the outcome of CheckMate-040 study, the FDA granted accelerated approval to nivolumab for the treatment of hepatocellular carcinoma (HCC) as second-line therapy in patients who have been previously treated with sorafenib.

CheckMate-459 is an ongoing phase III study, (NCT02576509) that randomizes patients with advanced HCC to either nivolumab or sorafenib in the first-line setting [37].

The efficacy and safety of pembrolizumab in HCC has been investigated. The phase I/II study KEYNOTE-224 tested pembrolizumab in 104 patients with advanced HCC who progressed on sorafenib. The overall response rate was 16.3%. Durable response was seen with 94% of responders were estimated to have a response duration of 6 months or longer. The median PFS was 4.8 months, and the median OS was not been reached. The safety profile was generally comparable to that established for pembrolizumab monotherapy in other indications, and no viral flares were seen [38].

4.2.2. Oncolytic immunotherapy

Targeting tumor vasculature by oncolytic viruses (OVs) is an attractive strategy that offers several advantages. Oncolytic viruses are wild-type or engineered viruses that selectively target and replicate in cancer cells and cause lysis without harming normal tissues [39]. The underlying mechanism of the antitumor activity for oncolytic viruses involves direct killing of tumor cells by expanding in the cells and causing cell lysis. Different from normal cell, viruses can expand in cancer cells considerably due to the impairment of the tumor's defense mechanisms against viral infection. [40–43]. In addition,, OVs can initiate antitumor immune response by

triggering key signals through oncolysis to dendritic cells (DCs) and other antigen-presenting cells (APCs) [44]. OVs have some advantages over other treatment modalities, those include: the low probability of generating resistance as OVs often target multiple oncogenic pathways; OVs replicate in a tumor-selective fashion with minimal systemic toxicities; and virus dose in the tumor increases over time due to in situ virus amplification, as opposed to classical drug pharmacokinetics that decreases with time [45]. The efficacy of an evolutionary cancer-favoring engineered vaccinia virus (CVV) was investigated in an animal model of metastatic HCC. In this animal study, the subjects were randomized into sorafenib, CVV, or sorafenib with CVV. Metastatic regions were interestingly rare in the CVV-treated groups (i.e., CVV or sorafenib with CVV) whereas metastatic regions existed in the sorafenib-treated group [46].

JX-594 is a thymidine kinase gene-inactivated oncolytic vaccinia virus engineered for the expression of transgenes encoding human granulocyte-macrophage-colony-stimulating factor (GM-CSF) and β-galactosidase, which increases antitumor immune responses [39, 47–49] This virus is safe in humans and extremely toxic to cancer cells.

Oncolytic viruses have produced enough therapeutic efficacy with great optimism in the future trials. Although the initial concerns of clinical investigators were for safety like a risk of viral infection or introduce oncogenic mutation, these have proven not to be a significant issue in these trials.

4.2.3. HCC vaccines

Cancer vaccination is performed by utilizing antigenic substances to stimulate tumor-specific immune responses that can remove cancer cells and prevent recurrences. HCC vaccines include cancer cells, antigen peptides, DCs, and DNA-based.

4.2.3.1. Antigen peptide vaccines

Peptide-based tumor-associated antigens (TAAs), such as alpha-fetoprotein (AFP), GPC3, SSX-2, NY-ESO-1, human telomerase reverse transcriptase (hTERT), HCA587, and melanoma antigen gene-A (MAGE-A), are excellent vaccine targets for the treatment of HCC [50].

AFP which normally originates from embryonic liver cells, can be overexpressed on HCC cell surfaces. However, immune responses to AFP are limited due to acquired immune tolerance during the development of the immune system. To overcome this tolerance, a research group investigated the use of a recombinant rat AFP to induce cross-reactions between xenografts and endogenous molecules in animals and observed modest cellular and humoral immune responses [51]. In a phase II trial of GPC3-derived peptide vaccine for HCC, 25 patients received 10 vaccinations over 1 year after surgery. The recurrence rate in patients who underwent both surgery and vaccination was significantly lower than the rate in 21 patients who underwent surgery only (24% vs. 48 and 52.4% vs. 61.9% at 1 and 2 years, $p = 0\ 047$ and 0.387, respectively), demonstrating the efficacy of the GPC3-derived vaccine [52].

4.2.3.2. Dendritic cell (DC) vaccines

DCs, were found to be the most powerful APCs in the body's immune system, and capable of stimulating naïve T cells and driving primary immune responses. A phase I/IIa comparative

study with 30 patients with advanced HCC stratified into mature autologous DCs pulsed, and other control group received supportive treatment. The result demonstrated an improvement in overall survival with two patients (13.3%) partial radiological response was observed, and nine patients (60%) has stable disease. The study concludes using tumor antigen-pulsed DCs vaccine can be effective adjuvant therapy with other treatment modalities of HCC or palliative treatment option in advanced HCC where other treatment options are not applicable [53]. In addition, the safety and tolerance of DC vaccines have been confirmed in patients with HCC [54].

4.3. Direct immunological strategy

4.3.1. Adoptive cell therapy

Adoptive cell therapy (ACT) is an immunotherapeutic approach that attacks cancer cells using genetically engineered patients' lymphocytes. It functions by stimulating or loading autologous lymphocytes with cytokines or tumor antigens, cultivating them ex vivo and then re-infusing them into the patient [55–57]. Adoptive immunotherapy for HCC includes cytokine-induced killer (CIK) cells, tumor-infiltrating lymphocytes (TILs), natural killer (NK) cells, and chimeric antigen receptor (CAR) T cells. The effectiveness and safety of ACT in patients with HCC have been studied in many experiments, which paved the road for its clinical implication.

4.3.1.1. Cytokine induced killer cells (CIK)

CIK cells are a heterogeneous MHC independent cell population which are able to both recognize tumor antigens and kill cancer cells directly [58, 59]. In a phase III study of adjuvant CIK therapy after radical resection for HCC, patients were randomized to receive four cycles of CIK therapy or no treatment. The median time to recurrence (TTR) was 13.6 months in the CIK group and 7.8 months in the control group ($p = 0.01$), All adverse events were grade 1 or 2. There were no significant differences in incidence between the two groups, indicating the safety and efficacy with respect to prolonging TTR of CIK therapy in patients with HCC. However, there were no statistically significant differences between the groups in disease-free survival (DFS) and overall survival (OS) [60]. In addition, a meta-analysis of 693 patients with HCC demonstrated that a combination of dendritic cell- (DC-) CIK cells and TACE improves 1-and 2-year OS, overall response rate (ORR), disease control rate (DCR), and the quality of life [61].

4.3.1.2. Tumor infiltrating lymphocytes (TILs)

TILs are autologous tumor-infiltrating lymphocytes (TIL), which are derived from tumor tissues and are cultured and induced using IL-2 and anti-CD3 antibodies ex vivo [62–64]. Reinfusion of autologous TILs, which possess tumor-specific immunity, may target multiple tumor antigens. Low toxicity of autologous TILs was verified in a phase I study involving patients with HCC, suggesting a novel treatment option [65]. To date, TILs have not been well characterized, mainly due to difficulties in purifying and expanding them.

4.3.1.3. Natural killer cells (NKCs)

NK cells are component of innate immune system and can directly kill tumor cells and infected cells without preliminary sensitization or MHC restriction [66]. However, they lack

the ability to target tumor cells and can injure normal liver tissues. In a previous series of experiments, the cytotoxicity of NK cells against HCC cells was enhanced by first generating a new hepatoma cell line, K562-mb15-41BBL, which achieved a more efficient stimulation of NK cells in vitro [67]. Furthermore, HCC cells exposed to 5 μmol/L sorafenib for 48 h showed high sensitivity to NK cells. Finally, NKG2D, an engineered NK-cell-activating receptor, was tested in vitro and in mice. All of the outcomes were positive in increasing the cytotoxicity of NK cells, providing the possibility of further clinical trials in HCC.

4.3.1.4. CAR-T cell

Chimeric antigen receptor redirected-T cells (CAR-T cells) are genetically modified T lymphocytes that specifically target tumor-associated antigens (TAAs) and kill cancer cells in an MHC-independent manner [68, 69]. CAR-T cells have achieved inspiring outcomes in patients with B cell malignancies with great therapeutic efficacy in leukemia and lymphoma therapy. CAR T therapy is being studied for solid tumors, such as HCC [70]. In some solid tumors with a tremendous phenotypic heterogeneity, CAR T cells could target the tumor antigen and cause antigen-positive cell death, while antigen-negative cancer cells may induce tumor relapse. However, Cart T cell structure engineering has been evolved significantly. Recently, CAR T cells with a transgenic "payload or TRUCK," also called the "fourth generation" CAR T cells, were designed [71]. This CAR T cells work by releasing inducible cytokines such as IL-12 which will augment T cell activation and further activate innate immune system to kill antigen negative cancer cells. Specific Tumor-associated antigens in HCC that recognized by cytotoxic T lymphocytes (CTLs) have been investigated. GPC3, which usually correlates with poor prognosis in HCC, has been demonstrated as a promising liver cancer-specific target in multiple studies, due to its overexpression in HCC and limited expression in normal tissues [72] GPC3-targeted CAR T cells could providing promising therapeutic intervention for GPC3-positive HCC. The ability of GPC3-targeted CAR T cells to eliminate GPC3-positive HCC cells was confirmed both in vivo and in vitro, and the survival of mice with HCC xenografts was prolonged with CAR T cell therapy in vivo [73]. In another study, T cells with two complementary CARs against GPC3 and asialoglycoprotein receptor 1 (ASGR1) decreased the risk of on-target, off tumor toxicities and demonstrated potent antitumor immune responses targeting $GPC3^{+}$ $ASGR1^{+}$ HCCs both in vivo and in vitro [74]. However, to date, the related studies conducted have been predominantly basic, and more clinical trials are required to prove the efficacy of CAR T in HCC.

4.4. Combination strategies

Combination therapies include combinations of different checkpoint inhibitors with TKIs, oncolytic viruses, small molecules and ablative therapies.

Combining anti-PD-1 with sorafenib has been studied in an animal model in HCC. The results showed efficacy only with the concomitant targeting of the hypoxic and immunosuppressive microenvironment with agents such as CXCR4 inhibitors, and not when combined with sorafenib alone [75]. According to these results, a potential future approach could be by careful titration of VEGF inhibition with the aim to block the VEGF pathway and contemporarily alleviate hypoxia by vascular normalization, enhancing immunotherapy efficacy [76].

http://dx.doi.org/10.5772/intechopen.79872

Checkpoint inhibitors combinations have also been studied, as a way to improve synergy and overcome resistance. PD-L1 is not the only immunosuppressive factor in the tumor microenvironment. The regulatory T cells (Treg) stands out among the immunosuppressive cells of the tumor microenvironment. Anti-CTLA-4 agents deplete tumor-associated Treg via an FccR dependant mechanism in preclinical models and have promising result in malignant melanoma [77].

5. Cytotoxic chemotherapies

Historically, traditional chemotherapeutic agents have not shown great efficacy in the treatment of HCC when used in the advanced disease stage, in particular in case of progression after locoregional therapy. Moreover, conventional cytotoxic chemotherapies have not provided a clinical benefit or prolonged survival for patients with advanced HCC. There are limited data supporting the use of cytotoxic chemotherapies in unresectable disease, and it should be used preferably in the context of a clinical trial [78].

6. Conclusions

Advanced HCC remains a deadly disease with limited systemic treatment options. The advent of sorafenib as first-line treatment ignited a plethora of trials testing various targeted and immunotherapeutic approaches. Currently, both regorafenib and nivolumab are FDA approved for second-line treatment among patients with advanced HCC who progressed

Agent	Type	MOA	FDA Approved	Line of treatment	Trial	Positive outcome	Ref.
Sorafenib	MKI	VEGFRs, PDGFR, TKI	Yes	First line	SHARP	OS, PFS	[3]
Lenvatinib	MKI	VEGFR, FGFR, PDGFRs, c-kit	No	First line	REFLECT	Non-inferior to sorafenib	[11]
Regorafenib	MKI	VEGFR, anti-stromal TKI	Yes	Second line	RESORCE	OS, DCR	[13]
Cabozantinib	MKI	VEGFR, MET, AXL c-KIT	No	Second or third line	CELESTIAL	OS	[15]
Nivolumab	IgG4 McA	Anti-PD-1	Yes	Second line	CheckMate-040	DCR, OS,PFS	[36]

List of abbreviations: MOA: mechanism of action, Ref: references, DCR: disease control rate, FGFR: fibroblast growth factor receptor, McA: monoclonal antibody, MKI: multi-tyrosine kinase inhibitor, OS: overall survival, PFS: progression free survival, PDGFR: platelet-derived growth factor receptor, PD-1: programmed death-1, TKI: trosine kinase inhibitor, VEGFRs: vascular endothelial growth factor receptors.

Table 1. Most common systemic agents for advanced HCC.

on sorafenib. The list of available treatment options (**Table 1**) is expected to increase with the encouraging results of several ongoing early phase trials, which eventually will lead to improvement in patients survivals.

Conflict of interest

Anwaar Saeed, MD declares research grants from AstraZeneca and Exelixis.

The remaining authors declare that they have no conflict of interests.

Author details

Mohammad Telfah, Mohammed Al-Jumayli and Anwaar Saeed*

*Address all correspondence to: asaeed@kumc.edu

Department of Medicine, Division of Medical Oncology, University of Kansas Medical Center Kansas City, Westwood, Kansas, USA

References

[1] SEER. Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. 2008-2014

[2] Chang YS et al. Sorafenib (BAY 43-9006) inhibits tumor growth and vascularization and induces tumor apoptosis and hypoxia in RCC xenograft models. Cancer Chemotherapy and Pharmacology. 2007;**59**(5):561-574

[3] Llovet JM et al. Sorafenib in advanced hepatocellular carcinoma. The New England Journal of Medicine. 2008;**359**(4):378-390

[4] Bruix J et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: Subanalyses of a phase III trial. Journal of Hepatology. 2012;**57**(4):821-829

[5] Cheng AL et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. The Lancet Oncology. 2009;**10**(1):25-34

[6] Pinter M et al. Sorafenib in unresectable hepatocellular carcinoma from mild to advanced stage liver cirrhosis. The Oncologist. 2009;**14**(1):70-76

[7] Abou-Alfa GK et al. Safety and efficacy of sorafenib in patients with hepatocellular carcinoma (HCC) and Child-Pugh A versus B cirrhosis. Gastrointestinal Cancer Research. 2011;**4**(2):40-44

[8] Abou-Alfa GK et al. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: A randomized trial. Journal of the American Medical Association. 2010;**304**(19):2154-2160

[9] Abou-Alfa GK, Niedzwieski D, Knox JJ. Phase III randomized study of sorafenib plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (HCC): CALGB 80802 (Alliance). Journal of Clinical Oncology. 2016;**34**(Suppl 4S; abstr 192)

[10] Ikeda K et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. Journal of Gastroenterology. 2017;**52**(4):512-519

[11] Kudo M et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet. 2018;**391**(10126):1163-1173

[12] Wilhelm SM et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. International Journal of Cancer. 2011;**129**(1):245-255

[13] Bruix J et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;**389**(10064):56-66

[14] Xiang Q et al. Cabozantinib suppresses tumor growth and metastasis in hepatocellular carcinoma by a dual blockade of VEGFR2 and MET. Clinical Cancer Research. 2014;**20**(11):2959-2970

[15] Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib: Results from the randomized phase III CELESTIAL trial (abstr). Journal of Clinical Oncology. 2018;**36**

[16] Kang YK et al. Randomized phase II study of axitinib versus placebo plus best supportive care in second-line treatment of advanced hepatocellular carcinoma. Annals of Oncology. 2015;**26**(12):2457-2463

[17] Faivre S et al. Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: An open-label, multicentre, phase II study. The Lancet Oncology. 2009; **10**(8):794-800

[18] Cheng A, Kang Y, Lin D, et al. Phase III trial of sunitinib versus sorafenib in advanced hepatocellular carcinoma (HCC) (Abstract 4000). Journal of Clinical Oncology. 2011; **29**(256s)

[19] Siegel AB et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. Journal of Clinical Oncology. 2008; **26**(18):2992-2998

[20] Sun W et al. Phase 2 trial of bevacizumab, capecitabine, and oxaliplatin in treatment of advanced hepatocellular carcinoma. Cancer. 2011;**117**(14):3187-3192

[21] Hsu CH et al. Efficacy and tolerability of bevacizumab plus capecitabine as first-line therapy in patients with advanced hepatocellular carcinoma. British Journal of Cancer. 2010;**102**(6):981-986

[22] Zhu AX et al. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. Journal of Clinical Oncology. 2006;**24**(12):1898-1903

[23] Zhu AX et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): A randomised, double-blind, multicentre, phase 3 trial. The Lancet Oncology. 2015;**16**(7):859-870

[24] Miamen AG, Dong H, Roberts LR. Immunotherapeutic approaches to hepatocellular carcinoma treatment. Liver Cancer. 2012;**1**(3-4):226-237

[25] Tsuchiya N et al. Potentiality of immunotherapy against hepatocellular carcinoma. World Journal of Gastroenterology. 2015;**21**(36):10314

[26] Fujiwara K et al. Decreased expression of B7 costimulatory molecules and major histocompatibility complex class-I in human hepatocellular carcinoma. Journal of Gastroenterology and Hepatology. 2004;**19**(10):1121-1127

[27] Henick BS, Herbst RS, Goldberg SB. The PD-1 pathway as a therapeutic target to overcome immune escape mechanisms in cancer. Expert Opinion on Therapeutic Targets. 2014;**18**(12):1407-1420

[28] Xie Y et al. Immunotherapy for hepatocellular carcinoma: Current advances and future expectations. Journalof Immunology Research. 2018;**2018**

[29] Hato T et al. Immune checkpoint blockade in hepatocellular carcinoma: Current progress and future directions. Hepatology. 2014;**60**(5):1776-1782

[30] Meng X et al. Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy. Cancer Treatment Reviews. 2015;**41**(10):868-876

[31] Vesely MD et al. Natural innate and adaptive immunity to cancer. Annual Review of Immunology. 2011;**29**:235-271

[32] Melero II et al. A clinical trial of Ctla-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. Immunology. 2012;**137**:54

[33] Duffy AG et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. Journal of Hepatology. 2017;**66**(3):545-551

[34] Shi F et al. PD-1 and PD-L1 upregulation promotes $CD8^+$ T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. International Journal of Cancer. 2011;**128**(4):887-896

[35] Gao Q et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clinical Cancer Research. 2009;**15**(3):971-979

[36] El-Khoueiry AB et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. The Lancet. 2017;**389**(10088):2492-2502

[37] Sangro B et al. A randomized, multicenter, phase 3 study of nivolumab vs sorafenib as first-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC): CheckMate-459. American Society of Clinical Oncology. 2016

[38] Zhu AX et al. KEYNOTE-224: Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib. American Society of Clinical Oncology. 2018

[39] Parato KA et al. The oncolytic poxvirus JX-594 selectively replicates in and destroys cancer cells driven by genetic pathways commonly activated in cancers. Molecular Therapy. 2012;**20**(4):749-758

[40] Hammill AM, Conner J, Cripe TP. Oncolytic virotherapy reaches adolescence. Pediatric Blood & Cancer. 2010;**55**(7):1253-1263

[41] Bourke M et al. The emerging role of viruses in the treatment of solid tumours. Cancer Treatment Reviews. 2011;**37**(8):618-632

[42] Platanias LC. Mechanisms of type-I-and type-II-interferon-mediated signalling. Nature Reviews Immunology. 2005;**5**(5):375

[43] Guo ZS, Thorne SH, Bartlett DL. Oncolytic virotherapy: Molecular targets in tumor-selective replication and carrier cell-mediated delivery of oncolytic viruses. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2008;**1785**(2):217-231

[44] Kaufman HL, Kohlhapp FJ, Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. Nature Reviews Drug Discovery. 2015;**14**(9):642

[45] Chiocca EA, Rabkin SD. Oncolytic viruses and their application to cancer immunotherapy. Cancer Immunology Research. 2014;**2**(4):295-300

[46] Yoo SY et al. Evolutionary cancer-favoring engineered vaccinia virus for metastatic hepatocellular carcinoma. Oncotarget. 2017;**8**(42):71489

[47] Breitbach CJ et al. A phase 2, open-label, randomized study of Pexa-Vec (JX-594) administered by intratumoral injection in patients with unresectable primary hepatocellular carcinoma. In: Gene Therapy of Solid Cancers. Springer; 2015. pp. 343-357

[48] Ady JW et al. Oncolytic immunotherapy using recombinant vaccinia virus GLV-1h68 kills sorafenib-resistant hepatocellular carcinoma efficiently. Surgery. 2014;**156**(2):263-269

[49] Wang J et al. Treatment of human hepatocellular carcinoma by the oncolytic herpes simplex virus G47delta. Cancer Cell International. 2014;**14**(1):83

[50] Sun T et al. Clinical research on dendritic cell vaccines to prevent postoperative recurrence and metastasis of liver cancer. Genetics and Molecular Research. 2015;**14**(4):16222-16232

[51] Zhang W et al. Immunotherapy of hepatocellular carcinoma with a vaccine based on xenogeneic homologous α fetoprotein in mice. Biochemical and Biophysical Research Communications. 2008;**376**(1):10-14

[52] Sawada Y et al. Phase II study of the GPC3-derived peptide vaccine as an adjuvant therapy for hepatocellular carcinoma patients. Oncoimmunology. 2016;**5**(5):e1129483

[53] El Ansary M et al. Immunotherapy by autologous dendritic cell vaccine in patients with advanced HCC. Journal of Cancer Research and Clinical Oncology. 2013;**139**(1):39-48

[54] Lee J-H et al. A phase I/IIa study of adjuvant immunotherapy with tumour antigen-pulsed dendritic cells in patients with hepatocellular carcinoma. British Journal of Cancer. 2015;**113**(12):1666

[55] Jixia Z, Chengyan Z, Pingli W. Advances in application of adoptive T-cell therapy for cancer patients. Journal of Zhejiang University (Medical Science). 2017;**46**(2):211-217

[56] Yeku O, Li X, Brentjens RJ. Adoptive T-cell therapy for solid tumors. In: American Society of Clinical Oncology Educational Book. American Society of Clinical Oncology. Meeting. NIH Public Access. 2017

[57] Baruch EN et al. Adoptive T cell therapy: an overview of obstacles and opportunities. Cancer. 2017;**123**(S11):2154-2162

[58] Longo V et al. Immunotherapeutic approaches for hepatocellular carcinoma. Oncotarget. 2017;**8**(20):33897

[59] Gao X et al. Cytokine-induced killer cells as pharmacological tools for cancer immunotherapy. Frontiers in Immunology. 2017;**8**:774

[60] Xu L et al. A randomized controlled trial on patients with or without adjuvant autologous cytokine-induced killer cells after curative resection for hepatocellular carcinoma. Oncoimmunology. 2016;**5**(3):e1083671

[61] Su Y et al. The efficacy and safety of dendritic cells co-cultured with cytokine-induced killer cell therapy in combination with TACE-predominant minimally-invasive treatment for hepatocellular carcinoma: a meta-analysis. Clinical Laboratory. 2016;**62**(4):599-608

[62] Toh U et al. Characterization of IL-2-activated TILs and their use in intrapericardial immunotherapy in malignant pericardial effusion. Cancer Immunology, Immunotherapy. 2006;**55**(10):1219-1227

[63] Yuan L et al. The preparation and study on hepatic targeting tendency of galactosyl-anti-CD3-McAb in mice. Hua Xi Yi Ke Da Xue Xue Bao (Journal of West China University of Medical Sciences). 2001;**32**(3):424-426

[64] Kikuchi T, Watanabe M, Ohno T. Cytological characteristics of human glioma-infiltrating lymphocytes stimulated with recombinant interleukin 2 and an anti-CD3 antibody. Cancer Science. 1991;**82**(3):339-345

[65] Jiang S-S et al. A phase I clinical trial utilizing autologous tumor-infiltrating lymphocytes in patients with primary hepatocellular carcinoma. Oncotarget. 2015;**6**(38):41339

[66] Narni-Mancinelli E, Vivier E, Kerdiles YM. The 'T-cell-ness' of NK cells: Unexpected similarities between NK cells and T cells. International Immunology. 2011;**23**(7):427-431

[67] Kamiya T, Chang Y-H, Campana D. Expanded and activated natural killer cells for immunotherapy of hepatocellular carcinoma. Cancer Immunology Research. 2016;**4**(7):574-581

[68] Abken H, Chmielewski M, Hombach AA. Antigen-specific T-cell activation independently of the MHC: Chimeric antigen receptor-redirected T cells. Frontiers in Immunology. 2013;**4**:371

[69] Li T, Wang H-T, Liu Z-G. Car technology and its application in treatment of multiple myeloma—Review. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2016;**24**(1):279-284

[70] Schuster SJ et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. New England Journal of Medicine. 2017;**377**(26):2545-2554

[71] Chmielewski M, Abken H. TRUCKs: The fourth generation of CARs. Expert Opinion on Biological Therapy. 2015;**15**(8):1145-1154

[72] Shirakawa H et al. Glypican-3 expression is correlated with poor prognosis in hepatocellular carcinoma. Cancer Science. 2009;**100**(8):1403-1407

[73] Gao H et al. Development of T cells redirected to glypican-3 for the treatment of hepatocellular carcinoma. Clinical Cancer Research. 2014;**20**(24):6418-6428

[74] Chen C et al. Development of T cells carrying two complementary chimeric antigen receptors against glypican-3 and asialoglycoprotein receptor 1 for the treatment of hepatocellular carcinoma. Cancer Immunology, Immunotherapy. 2017;**66**(4):475-489

[75] Chen Y et al. CXCR4 inhibition in tumor microenvironment facilitates anti-programmed death receptor-1 immunotherapy in sorafenib-treated hepatocellular carcinoma in mice. Hepatology. 2015;**61**(5):1591-1602

[76] Huang Y et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proceedings of the National Academy of Sciences. 2012;**109**(43):17561-17566

[77] Larkin J et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. New England Journal of Medicine. 2015;**373**(1):23-34

[78] Thomas MB et al. Systemic therapy for hepatocellular carcinoma: Cytotoxic chemotherapy, targeted therapy and immunotherapy. Annals of Surgical Oncology. 2008;**15**(4):1008-1014

IntechOpen