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ABOUT COVER

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AIMS AND SCOPE

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   WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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Research progress regarding programmed cell death 1/programmed cell death ligand 1 inhibitors combined with targeted therapy for treating hepatocellular carcinoma

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Abstract

In recent years, a number of targeted therapeutic agents have achieved success in phase III trials in patients with advanced hepatocellular carcinoma (HCC), including sorafenib, lenvatinib, and regorafenib. Immunotherapy is considered to be an effective treatment for advanced HCC. Immune checkpoint inhibitors targeting programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) are important antitumor immunotherapy agents that represent breakthroughs in the treatment of advanced HCC. However, treating advanced HCC is still a great challenge, and the need for new treatments remains urgent. This review briefly summarizes the research progress in the use of PD-1/PD-L1 inhibitors combined with targeted therapy for treating HCC.

Key Words: Programmed cell death 1/programmed cell death ligand 1 inhibitors; Targeted therapy; Hepatocellular carcinoma; Programmed cell death 1; Programmed cell death ligand 1

Core Tip: The incidence of liver cancer is high. Because the disease can develop rapidly, most patients progress to the intermediate or advanced stages and lose the

opportunity to undergo radical hepatectomy. Targeted therapy brings a glimmer of hope for patients with advanced hepatocellular carcinoma. Immunotherapy is a major focus in the field of tumor therapy, and it represents a breakthrough in the treatment of advanced hepatocellular carcinoma. The combination of programmed cell death 1/programmed cell death ligand 1 inhibitors and targeted therapy, to potentially achieve the superposition of 1 + 1 > 2 effects, is a promising strategy for treating cancer.

INTRODUCTION

Worldwide, liver cancer is the sixth most common cancer and the second leading cause of cancer-related deaths[1]. According to the global statistics of the International Agency for Research on Cancer, there were approximately 841000 new cases of liver cancer worldwide in 2018, the standardized incidence of liver cancer was 9.3/100000, there were approximately 782000 liver cancer deaths, and the average mortality rate of liver cancer was 8.5/100000, a figure that is on the rise[2]. The vast majority of primary liver cancers are hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and HCC-ICC. Among them, HCC accounts for more than 90% of cases[3]. HCC rarely shows specific or obvious symptoms in the early stage. Nearly 80% of patients with HCC have progressed to an advanced stage by the time of diagnosis and have lost the opportunity to undergo radical hepatectomy, which results in a poor prognosis and high mortality rate. Although progress has been made in early detection, most HCC patients are still diagnosed with advanced cancer[4].

The mainstay of systemic treatment for advanced HCC includes immunotherapy, chemotherapy, and targeted therapy. In recent years, a number of targeted therapeutic agents including sorafenib, lenvatinib, and regorafenib have achieved success in phase III trials of advanced HCC. Immunotherapy is considered to be an effective treatment for advanced HCC. Immune checkpoint inhibitors that target programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) are important antitumor immuno-therapeutics that represent a major breakthrough in the treatment of advanced HCC. Nivolumab and pembrolizumab have been approved by the United States Food and Drug Administration (FDA) as second-line treatments for HCC. This review briefly summarizes the research progress in the use of PD-1/PD-L1 inhibitors combined with targeted therapy in HCC.

PD-1/PD-L1 INHIBITORS AND LIMITATIONS

PD-1 is a type I transmembrane glycoprotein receptor and a member of the CD28/cytotoxic T-lymphocyte-associated protein (CTLA)-4 immune checkpoint receptor family. It is mainly expressed in T lymphocytes. Two binding ligands, PD-L1 and PD-L2, are members of the B7 family. They are widely expressed in human immune cells and some tissue cells, as well as in tumor cells[5]. Tumor cells express PD-L1, which binds to PD-1 on the surface of lymphocytes, inhibits the killing effect of lymphocytes and allows tumor cells to escape immune surveillance. PD-1/PD-L1 inhibitors block the binding of PD-1 to PD-L1, thereby terminate the negative regulatory signal in T cells, restore the activity of T cells, reverse the mechanism of tumor immune escape, reestablish the autoimmune response, and finally inhibit and kill tumor cells.

PD-1 inhibitors

Nivolumab: Nivolumab is the world's first recombinant human immunoglobulin (Ig)

G4 monoclonal antibody against PD-1. It can effectively block the PD-1/PD-L1 pathway and restore the antitumor effects of T cells. The CheckMate459 trial[6] is a randomized, global, multicenter phase III clinical trial of the efficacy and safety of nivolumab *vs* sorafenib as the first-line treatment for patients with unresectable HCC (uHCC). The median overall survival (mOS) of the nivolumab group was longer than that of the sorafenib group (16.4 mo *vs* 14.7 mo, $P = 0.0752$), but the difference in mOS did not reach the preset statistically significant threshold. The median progression-free survival (mPFS) was 3.7 mo in the nivolumab group compared to 3.8 mo in the sorafenib group, and the objective response rate (ORR) of the nivolumab group was approximately twice that of the sorafenib group (15% *vs* 7%). The rate of grade 3/4 treatment-related adverse events (TRAEs) was also lower in the nivolumab group than in the sorafenib group (22% *vs* 49%), and the percentage of patients who stopped treatment due to adverse events (AEs) was also lower (4% *vs* 8%). Although the primary endpoint (OS) of the nivolumab group did not reach statistical significance, the OS of the nivolumab group was clinically improved, with a high ORR and good tolerance. Therefore, nivolumab is safe and effective for treating advanced HCC, with manageable AEs.

Pembrolizumab: Pembrolizumab is the second PD-1 inhibitor approved by the US FDA for treating advanced HCC. The KEYNOTE-224 study is a non-randomized, global, multicenter, open-label phase II clinical trial on the efficacy of pembrolizumab in patients with advanced HCC who have previously been treated with sorafenib[7]. The mOS of the pembrolizumab group was 12.9 mo, the ORR was 17%, the disease control rate (DCR) was 64%, and the mPFS was 4.9 mo. The KEYNOTE-240 study[8] is a randomized, double-blind, phase III trial on the efficacy of pembrolizumab as a second-line treatment in patients with advanced HCC. The differences in the mOS (13.9 mo *vs* 10.6 mo, $P = 0.0238$) and mPFS (3.0 mo *vs* 2.8 mo, $P = 0.0022$) in the pembrolizumab group compared to the placebo group did not reach the preset thresholds for statistical significance ($P = 0.0174$ and $P = 0.0020$, respectively). The ORR in the pembrolizumab group was significantly higher than that in the placebo group (18.3% *vs* 4.4%, $P = 0.00007$), and the median duration of overall response (mDOR) was 13.8 mo in the pembrolizumab group compared to 10.6 mo in the placebo group. The safety was similar to that in previous studies of pembrolizumab. Regarding the OS and ORR, the results of the KEYNOTE-240 and KEYNOTE-224 studies were basically the same. The results of these two clinical trials once again confirmed the objective survival benefits of pembrolizumab. A phase III study (KEYNOTE-394) of pembrolizumab as a second-line treatment in Asian patients with HCC is currently under way.

Camrelizumab: Camrelizumab (SHR-1210) is a humanized anti-PD-1 monoclonal antibody. A phase II clinical study was performed to evaluate the efficacy of camrelizumab as a second-line treatment in Chinese patients with advanced HCC[9]. A total of 220 patients were enrolled, and 217 patients received treatment and were included in the analysis. The ORR was 13.8%, the mPFS was 2.1 mo, the DCR was 44.2%, the median time to response (mTTR) was 2.0 mo, the median time to progression (mTTP) was 2.6 mo, the 6-mo OS rate was 74.7%, the 12-mo OS rate was 55.9%, and the mOS was 13.8 mo. Camrelizumab is safe and well tolerated. The results reached the expected goal and confirmed that camrelizumab was effective in patients who had previously experienced failure of systemic therapy or found it intolerable. Camrelizumab has been approved as a second-line treatment for advanced HCC patients in China. It is anticipated that a phase III clinical trial will soon be carried out to improve the treatment of more patients with HCC.

PD-L1 inhibitors

There are few studies of PD-L1 inhibitors for treating HCC.

Durvalumab: Durvalumab is a humanized IgG1 monoclonal antibody against PD-L1. Phase I/II clinical trials of durvalumab for treating solid tumors have been completed. At the 2017 ASCO meeting, Wainberg *et al*[10] reported that 40 patients with advanced HCC who experienced failure of first-line treatment with sorafenib were treated with durvalumab. The mOS was 13.2 mo, the ORR was 10%, the DCR was 33.3%, and the rate of grade 3/4 AEs was 20%. Second-line treatment with durvalumab for advanced HCC is a promising strategy, and it continues to be studied.

Atezolizumab: Atezolizumab is a humanized IgG1 monoclonal antibody that can selectively target PD-L1 and block its interaction with PD-1 and the costimulatory molecule B7.1, thus it activates tumor-specific T cell immunity. The GO30140 study[11] is a global, multicenter, open-label phase Ib clinical trial. The basket design was used

in the study. Group A underwent a single-arm study on the safety and tolerance of atezolizumab plus bevacizumab as a first-line treatment for uHCC patients. The ORR was 36%, the DCR was 71%, the mPFS was 7.3 mo, the 6-mo PFS rate was 54%, the mOS was 17.1 mo, the 6-mo OS rate was 82%, and the 12-mo OS rate was 63% in group A. Group F underwent a controlled study. The patients were treated with atezolizumab or atezolizumab plus bevacizumab. The ORR of the atezolizumab group was 17%, and the mPFS was 3.4 mo in the atezolizumab group compared to 5.6 mo in the atezolizumab plus bevacizumab group [hazard ratio (HR) = 0.55, 95% confidence interval (CI): 0.4-0.74]. The treatment was well tolerated with controllable toxicity. No new safety signals were observed.

Limitations

The effective rate of PD-1/PD-L1 inhibitor monotherapy is low, and the ORR is 15%-20%. Most PD-1/PD-L1 inhibitors have only been assessed in phase I/II clinical trials, and phase III clinical trials have often failed to reach the preset statistical significance thresholds for their main endpoints. PD-1 inhibitors increase the incidence of interstitial pneumonia by blocking the binding of PD-1 to PD-L2[12]. PD-1/PD-L1 inhibitors are expensive. There are few studies on PD-L1 inhibitor monotherapy for HCC.

TARGETED THERAPY AND LIMITATIONS

Since 2007, sorafenib has been approved as a first-line treatment for advanced HCC. In the decade after this, clinical studies failed to provide evidence that any of the new molecular targeted drugs were more effective than or noninferior to sorafenib, but some of these new drugs were studied as second-line treatments after the failure of sorafenib. More specifically, drug development for HCC in the past 10 years has been marked by five failed global phase III trials (of sunitinib[13], brivanib[14], linifanib [15], erlotinib plus sorafenib[16], and sorafenib plus doxorubicin[17]) that did not show noninferiority or superiority to sorafenib in terms of OS as the first-line treatment of HCC. However, this situation changed after several clinical studies were conducted in 2017. The REFLECT study[18] showed that the efficacy of lenvatinib was noninferior to sorafenib as the first-line treatment for advanced HCC, and the RESORCE study[19] confirmed that regorafenib was beneficial as a second-line systemic targeted therapy for patients with HCC who progressed on sorafenib. Research on these agents provides renewed hope for the treatment of advanced HCC patients.

Sorafenib

Sorafenib, an oral tyrosine kinase inhibitor (TKI), is the only molecular targeted agent approved as a first-line treatment for advanced HCC. It can inhibit tumor cell proliferation and angiogenesis[20]. The SHARP study is a randomized, double-blind, placebo-controlled phase III clinical trial conducted in Europe and the United States [21]. The mOS (10.7 mo *vs* 7.9 mo, *P* < 0.001) and mTTP (5.5 mo *vs* 2.8 mo, *P* < 0.001) in the sorafenib group were significantly longer than those in the placebo group. An obvious curative effect was obtained in some patients in the sorafenib group. Subsequently, a randomized, double-blind, placebo-controlled phase III clinical study (the Oriental study) was conducted in the Asia-Pacific region[22]. The mOS (6.5 mo *vs* 4.2 mo, *P* = 0.014) and mTTP (2.8 mo *vs* 1.4 mo, *P* = 0.0005) in the sorafenib group were significantly longer than those in the placebo group. The most common any-grade AEs in the sorafenib group were hand-foot skin reaction (HFSR), diarrhea, hypertension, and anorexia. The results of these two clinical trials not only confirmed the survival benefits of sorafenib for treating advanced HCC patients but also proved its safety and good tolerance and established its status as a first-line treatment for patients with advanced HCC. Although sorafenib monotherapy has modest efficacy in HCC, with low ORR, PFS, and TTP, its manageable toxicity and mechanisms of action support a role for it in combination with other targeted agents. There are also second-line drugs available after the failure of first-line treatment or the emergence of drug resistance.

Lenvatinib

Lenvatinib is a TKI that can inhibit vascular endothelial-derived growth factor receptors (VEGFR) 1-3 and fibroblast growth factor receptors (FGFR) 1-4, thereby inhibiting angiogenesis and cell proliferation[23]. The REFLECT study[18] is a

randomized, global, multicenter, noninferiority phase III study of the efficacy of lenvatinib *vs* sorafenib as the first-line treatment for uHCC patients. The mOS noninferiority margin was set at 1.08. The mOS in the lenvatinib group met the criteria for noninferiority to sorafenib (13.6 mo *vs* 12.3 mo, 95%CI: 0.79-1.06). The mPFS, mTTP, and ORR in the lenvatinib group were significantly greater than those in the sorafenib group (7.4 mo *vs* 3.7 mo; 8.9 mo *vs* 3.7 mo; 24.1% *vs* 9.2%). The most common any-grade AEs in the lenvatinib group were hypertension (42%), diarrhea (39%), decreased appetite (34%), and decreased weight (31%). In short, in terms of OS, lenvatinib was noninferior to sorafenib, and there were statistically and clinically significant improvements in PFS, TTP, and ORR. Additionally, no new safety signals were found. Although lenvatinib did not achieve superiority to sorafenib, lenvatinib was better tolerated, and the PFS, TTP, and ORR were significantly increased. It is expected that in the future, lenvatinib will be more widely adopted for treating advanced HCC patients and will become an important treatment option for this patient group.

Regorafenib

Regorafenib is an oral TKI with a similar structure to sorafenib, and its targets include a variety of kinases in the signaling pathways involved in angiogenesis and tumor growth. The RESORCE study is a randomized, double-blind, placebo-controlled, global, multicenter, phase III clinical trial on the efficacy and safety of regorafenib in patients with HCC who have previously been treated with sorafenib[19]. The mOS in the regorafenib group was significantly longer than that in the placebo group (10.6 mo *vs* 7.8 mo, HR = 0.36), the risk of death was reduced by 37% in the regorafenib group, and the mPFS, TTP, and ORR in the regorafenib group were significantly greater (3.1 mo *vs* 1.5 mo; 3.2 mo *vs* 1.5 mo; 11% *vs* 4%). The most common any-grade AEs in the regorafenib group were hypertension, HFSR, fatigue, and diarrhea. Regorafenib is safe and well tolerated. Exploratory analysis in the RESORCE study showed that sequential therapy with sorafenib and regorafenib resulted in a better survival time (26.0 mo in the sorafenib and regorafenib sequential therapy group *vs* 19.2 mo in the placebo group)[24]. Thus, regorafenib is expected to replace sorafenib and be used in combination with other targeted agents for treating advanced HCC patients who cannot tolerate sorafenib and provide new alternative regimens for assessment in clinical trials.

Cabozantinib

Cabozantinib is a TKI that targets MET, VEGFR1/2/3, ROS1, RET, AXL, NTRK, and KIT[25]. The CELESTIALI study[26] is a global, randomized, double-blind phase III clinical trial to evaluate the efficacy and safety of cabozantinib *vs* placebo for treating advanced HCC patients. The mOS (10.2 mo *vs* 8.0 mo, *P* = 0.005), mPFS (5.2 mo *vs* 1.9 mo, *P* < 0.001), and ORR (4.0% *vs* 0.4%, *P* = 0.009) in the cabozantinib group were significantly better than those in the placebo group. The common grade 3/4 AEs in the cabozantinib group included HFSR (17%), hypertension (16%), transaminase increase (12%), fatigue (10%), and diarrhea (10%). It was well tolerated, and its safety was controllable.

Limitations

New targeted agents continue to emerge. Although many agents have shown excellent therapeutic effects in phase I and II clinical trials, many have not been successful in phase III clinical trials[27]. Resistance against targeted agents develops easily, their duration of effectiveness is short, and it is difficult to control the course of the disease. Predictive biomarkers of targeted agents have not been found[28].

PD-1/PD-L1 INHIBITORS COMBINED WITH TARGETED THERAPY

Targeted therapy takes effect quickly, and the ORR is relatively high, but these treatments produce resistance, and the duration of the effect is short. PD-1/PD-L1 inhibitor monotherapy has a longer duration of efficacy, but the efficacy is lower, and the ORR is only 15%-20%. If the advantages of the two are combined, complementary effects may be produced. In other words, combining PD-1/PD-L1 inhibitors and targeted therapy is a promising combination strategy that can potentially achieve a superposition of 1 + 1 > 2 effects. The combination of PD-1/PD-L1 inhibitors and targeted therapy was selected according to the results of the phase III trials from the website for clinical trials (World Health Organization-International Clinical Trials

Registry Platform websites, and clinicaltrials), and the results showed that its trials made progress in the treatment of advanced HCC (Tables 1 and 2).

Phase I/II trials

Lenvatinib plus pembrolizumab: In an HCC mouse model, the combination of lenvatinib and a PD-1 inhibitor significantly reduced the proportion of monocytes and macrophages, increased the proportions of early activated and effector CD8+ T cells, and enhanced antitumor activity of the PD-1 inhibitor[38]. In theory, the immunomodulatory effect of lenvatinib can supplement the activity of pembrolizumab, thus it can increase the sensitivity of tumors to this combination therapy. A phase Ib study (KEYNOTE-524)[29] was conducted to evaluate the tolerance and safety of lenvatinib plus pembrolizumab in patients with uHCC. The study consisted of two phases: A dose-limited toxicity (DLT) phase and an expansion phase. A total of 100 patients were included. The ORR was 46% based on modified response evaluation criteria in solid tumors (mRECIST) and 36% based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) with independent imaging review (IIR). The complete response (CR) was 11% and 1% based on IIR, the mPFS was 9.3 and 8.6 mo based on IIR, the mDOR was 8.6 and 12.6 mo based on IIR, the mTTR was 1.9 and 2.8 mo based on IIR, the mOS was 22 mo (95%CI: 20.4-NE), the 6-mo OS was 81%, and the 12-mo OS rate was 67.5%. According to the RECIST criteria, progressive disease (PD) is defined as a ≥ 20% increase in the sum of the longest diameter of target lesions, partial response (PR) is defined as a ≥ 30% decrease in the sum of the longest diameter of target lesions, CR is defined as the absence of target lesions, and stable disease (SD) is defined as insufficient increase/decrease to qualify as PD/PR[39]. As seen from waterfall plots of the changes in the diameters of target lesions, most patients achieved PR. Thus, the data and plots confirmed that lenvatinib plus pembrolizumab has antitumor activity in uHCC. The most common TRAEs of lenvatinib plus pembrolizumab were hypertension (36%), diarrhea (35%), fatigue (30%), decreased appetite (28%), and hypothyroidism (25%). The most common grade 3 TRAE was hypertension (17%). The only grade 4 TRAE was leukopenia/neutropenia. In short, lenvatinib plus pembrolizumab showed antitumor activity, the toxicity was controllable, and there were no unexpected safety signals.

Lenvatinib plus nivolumab: Study-117 is an open-label phase Ib study of the tolerance and safety of lenvatinib plus nivolumab in patients with uHCC[30]. A total of 30 patients participated in the trial (part I, *n* = 6, patients who were not suitable for other treatments due to multiline drug resistance; part II, *n* = 24, patients who had not previously received treatment for uHCC). The main endpoints were tolerance and safety. According to the mRECIST criteria, the ORR of the total population was 76.7%, the DCR was 96.7%, the CR rate was 10%, the PR rate was 66.7%, the SD rate was 20%, and the clinical benefit rate (CBR) was 83.3%. In part II of the trial, according to the mRECIST criteria, the CR rate was 12.5% and 8.3%, as assessed by the investigator and the independent review committee, respectively. The CBR was 83.3% and 70.8%, the PR rate was 66.7% and 58.3%, the SD rate was 16.7% and 25%, the ORR was 79.2% and 66.7%, and the DCR was 95.8% and 91.7%, respectively. Lenvatinib plus nivolumab was well tolerated in patients with HCC and had antitumor activity. The efficacy of this regimen was considerable, with an ORR of 76.7%. Additionally, AEs were effectively controlled by dose adjustment, interruption, and supportive drug therapy.

Avelumab plus axitinib: Avelumab is a fully human anti-PD-L1 monoclonal antibody, and axitinib is a TKI that selectively inhibits VEGFR1/2/3. The VEGF Liver 100 study is a phase Ib clinical study of the tolerance and safety of avelumab plus axitinib for treating advanced HCC[31]. A total of 22 patients were included. According to the RECIST/mRECIST criteria, tumor shrinkage (shown in waterfall plots) was observed in 15 cases (68.2%) and 16 cases (72.7%), the ORR was 13.6% and 31.8%, and the mPFS was 5.5 and 3.8 mo, respectively. The mOS was 12.7 mo. The most common grade 3 TRAEs were hypertension (50.0%) and HFSR (22.7%), and no grade 4/5 TRAEs occurred. The most common immune-related AEs (irAEs) were hypothyroidism (31.8%) and hyperthyroidism (13.6%), and no grade 3 irAEs occurred. No patient stopped treatment due to TRAEs or irAEs. Overall, avelumab plus axitinib for the first-line treatment of HCC has controllable safety and obvious antitumor activity, and the ORR is higher than that for monotherapy.

Regorafenib plus pembrolizumab: The KN-743 study is a phase Ib study of the safety and tolerance of pembrolizumab plus regorafenib for treating advanced HCC[32]. A total of 36 patients who had not previously received systemic treatment and had Barcelona Clinic Liver Cancer (BCLC) stage B/C and Child-Pugh grade A were

Table 1 Combination therapy for hepatocellular carcinoma

Combination therapy	Trial name	Phase	Number of patients	Control	Outcome (months or rate)	Ref.
Lenvatinib + pembrolizumab	KEYNOTE-524	Ib	100	None	ORR: 46% by mRECIST and 36% by RECIST v1.1; mPFS: 9.3 mo by mRECIST and 8.6 mo by RECIST v1.1; mOS: 22.0 mo	Finn *et al*[29]
Lenvatinib + nivolumab	Study-117	Ib	30	None	ORR: 76.7%, DCR: 96.7%, CBR: 83.3%	Kudo *et al*[30]
Avelumab + axitinib	VEGF liver-100	Ib	22	None	mOS: 12.7 mo, 1-yr OS rate: 54.5%; ORR: 13.6% by RECIST v1.1 and 31.8% by mRECIST	Kudo *et al*[31]
Pembrolizumab + regorafenib	KN-743	Ib	36	None	ORR: 28%, DCR: 91%	Galle *et al*[32]
Camrelizumab + apatinib	RESCUE	II	190	None	ORR for first- and second-line treatment: 34.3% and 22.5%, mPFS: 5.7 and 5.5 mo; 12-mo OS rate: 74.7% and 68.2%	Xu *et al*[33]
Atezolizumab + bevacizumab	IMbrave150	III	501	Sorafenib	mOS: 19.2 mo *vs* 13.4 mo; mPFS: 6.9 mo *vs* 4.3 mo	Finn *et al*[34]
Lenvatinib + pembrolizumab	LEAP-002	III	750	Lenvatinib + placebo	Ongoing	Llovet *et al*[35]
camrelizumab + apatinib	NCT03764293	III	510	Sorafenib	Ongoing	National Cancer Institute[36]
Cabozantinib + atezolizumab	COSMIC-312	III	740	Sorafenib or cabozantinib	Ongoing	Kelley *et al*[37]

CBR: Clinical benefit rate; DCR: Disease control rate; HCC: Hepatocellular carcinoma; HR: Hazard ratio; MOS: Median overall survival; MPFS: Median progression-free survival; MRECIST: Modified response evaluation criteria in solid tumors; RECIST v1.1: Response evaluation criteria in solid tumors version 1.1; NE: Not estimable; ORR: Objective response rate; OS: Overall survival; VEGF: Vascular endothelial-derived growth factor.

Table 2 Grade 3/4 adverse events in combination therapy groups

Combination therapy group	Phase	Grade 3/4 adverse events (%)
Lenvatinib + pembrolizumab group (*n* = 100)	Ib	Hypertension (17), AST increased (11), diarrhea (5), asthenia (5), fatigue (4)
Lenvatinib + nivolumab group (*n* = 30)	Ib	Palmar-plantar erythrodysesthesia (56.7), dysphonia (53.3)
Avelumab + axitinib group (*n* = 22)	Ib	Hypertension (50.0), HFSR (22.7)
Pembrolizumab + regorafenib group (*n* = 36)	Ib	AST increase (19), ALT increase (14), hypertension (14), bilirubin increase (14), lipase increase (11)
Camrelizumab + apatinib group (*n* = 190)	II	Hypertension (34.2), gamma-glutamyltransferase increase (11.6), neutropenia (11.1)
Atezolizumab + bevacizumab group (*n* = 329)	III	Hypertension (15.2), AST increase (7.0), ALT increase (3.6), platelet count decrease (3.3), proteinuria (3.0)
Lenvatinib + pembrolizumab group	III	Ongoing
Camrelizumab + apatinib group	III	Ongoing
Cabozantinib + atezolizumab group	III	Ongoing

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HFSR: Hand–foot skin reaction.

included. The study included two stages: A DLT stage and an expansion stage. Overall, the median duration of treatment with regorafenib was 2.5 mo (0.2-15.9 mo) and that of pembrolizumab was 3.5 mo (0.03-19.2 mo). Of the 32 patients who could be included in the evaluation of the curative effect, 9 (28%) reached PR, 20 (63%) reached SD, and 2 (6%) reached PD. The most common grade 3 TRAEs were aspartate aminotransferase (AST) increase (19%), alanine aminotransferase (ALT) increase (14%),

hypertension (14%), bilirubin increase (14%), and lipase increase (11%). The safety of pembrolizumab plus regorafenib is controllable, and there is antitumor activity.

Camrelizumab plus apatinib: In a phase I clinical trial of camrelizumab plus apatinib for treating HCC, gastric cancer, and esophageal cancer[40], 43 patients were included. Among the 18 hepatitis B virus (HBV)-related HCC patients, the ORR was 50%, DCR was 93.8%, mPFS was 5.8, and mOS was not achieved in the 16 patients who could be included in the evaluation of the efficacy. The RESCUE study[33] was conducted to evaluate the efficacy and safety of camrelizumab plus apatinib for treating advanced HCC patients. The study is a non-randomized, open-label, multicenter, phase II clinical trial involving 70 patients with advanced HCC who had not previously received treatment and 120 patients who were refractory/intolerant to first-line targeted therapies. The ORR of patients treated with camrelizumab plus apatinib as first- and second-line treatments was 34.3% and 22.5%, the mPFS was 5.7 and 5.5 mo, the 9-mo OS rate was 86.7% and 79.1%, the 12-mo OS rate was 74.7% and 68.2%, and the 18-mo OS rate was 58.1% and 56.5%, respectively. The most common TRAEs were hypertension (72.6%), AST increase (63.2%), proteinuria (61.6%), and hyperbiliru-binemia (61.6%). There were reports of grade ≥ 3 TRAEs in 77.4% of cases, of which hypertension was the most common (34.2%). There were also reports of irAEs in 27.9% of cases, of which hypothyroidism (8.4%), rash (3.7%), and hyperglycemia (3.2%) were the most common. The incidence of reactive cutaneous capillary endothelial prolif-eration, a unique AE caused by camrelizumab, was significantly decreased in the camrelizumab plus apatinib group. Therefore, camrelizumab plus apatinib shows promising efficacy and manageable safety in patients with advanced HCC.

Phase III trials

Atezolizumab plus bevacizumab: Bevacizumab is a type of anti-VEGF monoclonal antibody that inhibits angiogenesis and tumor growth. It is the first agent to be used as an antitumor agent based on its inhibition of angiogenesis. In the treatment of tumors with bevacizumab plus atezolizumab (which targets PD-L1), bevacizumab can further enhance the effectiveness of atezolizumab by reversing VEGF-mediated immunosup-pression and promoting T cell infiltration into tumors by tumor vascular normal-ization[41]. The phase Ib GO30140 study [11] showed that atezolizumab plus bevacizumab has good tolerance, safety, and antitumor activity in patients with advanced HCC. Based on these results, a global, multicenter, open-label phase III clinical study (IMbrave150) was conducted to evaluate the efficacy and safety of atezolizumab plus bevacizumab (A + T) compared to standard therapy (sorafenib) as the first-line treatment in patients with uHCC[42]. A total of 501 patients were randomly assigned to the A + T group (*n* = 336) or the sorafenib group (*n* = 165) at a ratio of 2:1. The primary endpoints of the trial were OS and PFS, and the secondary endpoints were ORR and DOR. The mOS (NE *vs* 13.2 mo), 6-mo OS rate (84.8% *vs* 72.2%), and 12-mo OS rate (67.2% *vs* 54.6%) in the A + T group were greater than those in the sorafenib group. The mPFS (6.8 mo *vs* 4.3 mo) and the 6-mo PFS rate (54.5% *vs* 37.2%) in the A + T group were greater than those in the sorafenib group. In terms of the secondary endpoints, the ORR (27.3% *vs* 11.9%) and DCR (73.6% *vs* 55.3%) in the A + T group were higher than those in the sorafenib group. The median time to deteri-oration of quality of life in the A + T group was longer than that in the sorafenib group (11.2 mo *vs* 3.6 mo) and improved the quality of life of the patients. The study also released data on the Chinese subgroup. The Chinese patients in the A + T subgroup had higher rates of HBV infection, macrovascular invasion/extrahepatic metastasis, alpha fetoprotein ≥ 400 ng/mL, and other adverse prognostic factors, and the mOS of the Chinese patients in the A + T subgroup was NE *vs* 11.4 mo (HR = 0.44, 95%CI: 0.25-0.76), which reduced the risk of death by 56%. The PFS of the Chinese patients in the A + T subgroup was 5.7 mo compared to 3.2 mo in the sorafenib subgroup (HR = 0.60, 95%CI: 0.40-0.90). The 6-mo OS rate reached 87% in the Chinese A + T subgroup, which was better than that in the whole A + T group (84.8%). The most common TRAEs in the A + T group were hypertension (29.8%), fatigue (20.4%), proteinuria (20.1%), and AST increase (19.5%). The safety of A + T was consistent with the known safety profile, with no new safety signals. In short, A + T therapy exhibited statistically and clinically significant improvements in OS and PFS, and the 12-mo OS rate of the patients increased to 67.2%. After an additional 12-mo follow-up[34], the mOS was 19.2 mo in the A + T group compared to 13.4 mo in the sorafenib group (HR = 0.66, 95%CI: 0.52-0.85), and the mPFS was 6.9 mo in the A + T group compared to 4.3 mo in the sorafenib group (HR = 0.65, 95%CI: 0.53-0.81). The mOS of the Chinese patients was 24.0 mo in the A + T subgroup compared to 11.4 mo in the sorafenib group (HR =

0.53, 95%CI: 0.35-0.80). The A + T subgroup continued to show consistent and clinically significant treatment benefits. A + T therapy represents the main breakthrough in HCC treatment over the last decade or more. These results further support the use of A + T as a first-line treatment in patients with uHCC.

Lenvatinib plus pembrolizumab: The LEAP-002 study[35] is an ongoing multicenter, double-blind, randomized, controlled, phase III study of lenvatinib plus pembrolizumab *vs* lenvatinib plus placebo as the first-line treatment for uHCC. The study included 750 patients with BCLC stage B/C HCC for whom radical local therapy was not suitable. They were randomly divided into the two groups at a ratio of 1:1. The primary endpoints are OS and PFS. The patients have been enrolled in the groups and are currently being followed.

Camrelizumab plus apatinib: A global, open-label, multicenter, phase III clinical study of camrelizumab plus apatinib *vs* sorafenib as the first-line treatment for advanced HCC is currently underway[36], the results of which are anticipated. A total of 550 patients are scheduled to be enrolled (350 cases in China and 200 cases in the United States and Europe). The primary endpoints are OS and PFS.

Cabozantinib plus atezolizumab: The COSMIC-312 study[37] is an ongoing global, randomized, open-label phase III trial to evaluate the efficacy and safety of the first-line therapy with cabozantinib plus atezolizumab *vs* sorafenib or cabozantinib in patients with advanced HCC. Approximately 740 eligible patients with advanced HCC have been randomized at a 2:1:1 ratio to receive cabozantinib plus atezolizumab, sorafenib, or cabozantinib.

ADVERSE EVENTS

Immune checkpoint inhibitors combined with targeted therapy can improve the curative effect of treatment. However, AEs are also increased, which necessitates additional caution in clinical settings. If doctors find a need for a new type of immunotherapy for a patient with HCC, they should conduct a detailed evaluation of the tumor type, tumor localization, number of tumors, and gene mutations and treat the patient under the guidance of a clinical oncologist to reduce the risk of serious AEs.

Immune checkpoint inhibitor therapy can cause irAEs, which are usually temporary but can sometimes be severe or fatal[43]. The most common irAEs in patients treated with immune checkpoint inhibitors are skin toxicity (28%-50% reported itching, rash, and/or eczema), diarrhea (8%-19%, generally mild to moderate), colitis (1.3%, increased to 11.8% under combination therapy), hepatotoxicity (< 5%), immune-associated nonspecific interstitial pneumonia (approximately 10%), and endocrine diseases [commonly manifest as hypophysitis or thyroid dysfunction with autoimmune-mediated endocrine toxicity of the thyroid in grade 1-2 hypothyroidism (4%-8%), hyperthyroidism (2%-3%), and rare acute thyroiditis (1%)]. Other rare toxicities include nephrotoxicity (immune-mediated glomerulonephritis and renal insufficiency, approximately 1%), pancreatic toxicity (approximately 1%-2%), ophthalmic toxicity, arthritis, and nervous system abnormalities.

AEs caused by targeted therapy can be divided into fatal and nonfatal AEs[44]. Nonfatal AEs include skin reactions (HFSR, rash, and stomatitis), digestive tract reactions (diarrhea, nausea, vomiting, abdominal pain, and abdominal distension), cardiovascular reactions (hypertension and cardiotoxicity), liver function damages (liver cirrhosis and chronic hepatitis), and other reactions (fatigue, hemocytopenia, weight loss, headache, muscle soreness, hoarseness, and other flu-like symptoms). Fatal AEs include congestive heart failure, cerebral infarction, hemorrhage, liver failure, intestinal perforation, myocardial infarction, respiratory failure, pulmonary infarction, sepsis, and sudden death. The incidence of fatal AEs is very low.

Clinicians should be highly vigilant and pay attention not only to the antitumor effect but also to the AEs. They should fully understand the common AE types, grades, diagnosis, and treatment methods, ensure early AE diagnosis and early treatment, and control the AEs at a low level to reduce risks and improve the prognosis.

DISCUSSION

The incidence of HCC is high, with a high degree of heterogeneity. The proportion of HCC patients with BCLC stage B/C is also high, and the treatment is complicated. We

still need to thoroughly understand the molecular mechanisms of immunotherapy, rationally design clinical studies, and actively explore combinations of various immune-regulatory agents or immunotherapy with other treatment modalities to significantly improve the survival time and quality of life of patients with advanced HCC. In the coming years, research hotspots will include identifying sensitive biomarkers of efficacy and drug resistance and screening for patients with these biomarkers to achieve individualized treatment, more precise use of targeted therapy, and timely modifications of treatment plans.

Immunotherapy combined with targeted therapy is promising, but the best combination therapy agents need to be further explored. At present, several phase III studies are underway. Combination therapy assessment requires a larger sample size. In addition, optimal selection of combination therapy agents relies on the results of future phase III studies.

In this era of emphasis on precision medicine, it is imperative to identify appropriate predictive markers of efficacy. Identifying clinical indicators and serum or tissue biomarkers is essential, as they will allow specific effective drugs to be selected for individualized treatment of each HCC patient. At present, there are still no clear indexes for selecting an enriched target population or for predicting the prognosis or the curative effect[45].

Understanding mechanisms of resistance to anti-PD-1/PD-L1 agents is indispensable to improve outcomes by using combination therapies[46].

In HCC patients with HBV infection, lenvatinib seems to be more effective than sorafenib, and sorafenib seems to be more effective in HCC patients with HCV infection than in patients with other risk factors. There are currently no prospective studies on the effects of molecular targeted therapy based on the etiology of liver cancers.

CONCLUSION

Overall, PD-1/PD-L1 inhibitors combined with targeted therapy represent potentially beneficial regimens. With continued research, more effective immunotherapy combined with targeted therapy is expected in the future.

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