

Clinical outcomes and influencing factors of PD-1/PD-L1 in hepatocellular carcinoma (Review)

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Abstract. Hepatocellular carcinoma (HCC) has an increasing incidence worldwide, and the global 5-year survival rate ranges from 5-30%. In China, HCC seriously threatens the nation's health; the incidence of HCC ranks fourth among all theriomias, and the mortality rate is the third highest worldwide. The main therapies for HCC are surgical treatment or liver transplantation; however, most patients with HCC will experience postoperative recurrence or metastasis, eventually resulting in mortality. As for advanced or unresectable HCC, the current appropriate treatment strategy is transarterial chemoembolization; however, limited therapeutic effect and natural or acquired drug resistance affect the efficacy of this approach. Previous studies have demonstrated that PD-L1 expression on host cells and myeloid cells plays an important role in PD-L1 blocked-mediated tumor regression. Thus, further research on programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) is required. Countries including the United States, France, Britain and China have developed PD-1/PD-L1 blockers, including nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab, durvalumab, toripalimab, sintilimab and camrelizumab. Notably, all of these blockers have therapeutic effect and influencing factors in HCC. Factors that influence the clinical outcome of PD-1 have also been discovered, such as inflammatory genes, specific receptors and signaling pathways. The discovery of these factors will help to identify novel methods, such as combination treatment, to decrease the influence of other factors on the efficacy of PD-1/PD-L1. Sorafenib and lenvatinib have been approved for first-line treatment for patients with advanced HCC. When first-line treatment frequently fails,

pembrolizumab and ipilimumab plus nivolumab are used following sorafenib (but not lenvatinib) treatment in advanced HCC. Thus, tumor immunotherapy using PD-1/PD-L1 blockers exhibits promising outcomes for the treatment of HCC, and more novel PD-1/PD-L1 inhibitors are being developed to fight against this disease. The present review discusses the clinical results and influencing factors of PD-1/PD-L1 inhibitors in HCC to provide insight into the development and optimization of PD-1/PD-L1 inhibitors in the treatment of HCC.

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1. Introduction

Hepatocellular carcinoma (HCC) is a fatal malignancy originating in hepatocytes (1). HCC accounts for 90% of primary liver cancers (2), whereby 850,000 new cases of HCC and 745,500 mortalities are annually reported worldwide (3). In China, there are nearly 466,000 new cases of HCC and 422,000 mortalities per year (4), and only 10-15% of patients meet conditions for surgical excision due to the severity of HCC (5). In advanced HCC, surgical treatment becomes infeasible due to the spread of the tumor beyond the liver. The current recommended treatment strategy in advanced disease is transarterial chemoembolization (TACE); however, most patients with HCC have primary or acquired drug resistance, which affects the efficacy of TACE (6). Thus, it is important to identify chemotherapeutic drugs aimed at novel targets to ameliorate chemotherapeutic resistance.

Immune blockade inhibitors, also known as immune checkpoint inhibitors (ICIs), are a novel type of monoclonal antibody drug that can inhibit the function of inhibitory immune receptors to evoke an immune antineoplastic response (7). In principle, this interaction can be used to treat different types

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of cancer, including lung cancer, melanoma, urothelial and renal carcinomas, Hodgkin's lymphoma and gastrointestinal cancers (8). Several clinical trials have investigated the potential of similar treatments for HCC (9). The efficacy of single drugs is limited, and various clinical trials are investigating the potential combination of different ICIs or the combination of ICIs and target agents (7).

Amongst the numerous checkpoint molecules, the most widely studied, and those with the greatest clinical implications in human cancer, are cytotoxicity T lymphocyte protein 4 (CTLA-4), programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) (9). PD-L1 is expressed on immune cells and tumor cells, and tumor cells use PD-L1 to bind to PD-1 of T cells to 'cheat' the T cells and escape recognition, enabling them to continue to spread in the body. PD-L1/PD-1 antibodies can help T cells to evade this strategy and retain their ability to identify and kill tumor cells (10).

The present review discusses recent progress in clinical outcomes and influencing factors of PD-1/PD-L1 inhibitors, providing references and inspirations for the treatment of HCC.

2. Listed drugs

The National Comprehensive Cancer Network (NCCN) guidelines (2019) on HCC recommend sorafenib [Child-Pugh A (Class 1 evidence) or B7] and lenvatinib (Child-Pugh A only) for first-line systematic therapy. Another targeted drug that can be used for first-line treatment is linifanib. The objective response rate (ORR) of linifanib is higher than that of sorafenib; however, no significant difference between the survival rates achieved by these drugs has been observed, thus, the guide does not recommend the use of linifanib (11). A total of two drugs were recommended in the guidelines (2019) as second-line treatments, namely nivolumab and pembrolizumab (11).

PD-1 receptor blockers

Nivolumab. Nivolumab (Opdivo) was developed by Bristol-Myers Squibb and exhibits high affinity and specific targeting of an epitope of PD-1 (12,13). In September 2017, nivolumab received an accelerated approval for patients with HCC pretreated with sorafenib, based on the results of the phase I/II dose escalation and expansion cohort of the Checkmate-040 trial (14). The incidence of severe adverse events associated with grade 3/4 treatment was 4% (15). The latest results were reported in January 2018 at the American Society of Clinical Oncology GI annual meeting, based on 154 sorafenib-treated patients, with the conclusion that nivolumab has a significant effect in patients with HCC, with sorafenib pretreatment (16). The randomized phase III CheckMate 459 trial was performed to assess nivolumab vs. sorafenib as a first-line treatment in unresectable HCC; however, the result did not reach the specified end point (17). Although the results failed to meet the predefined threshold of statistical significance, the overall survival rate with nivolumab was significantly higher compared with sorafenib (18). Regorafenib vs. nivolumab following sorafenib failure in patients with HCC suggests that survival outcomes do not differ significantly (19). However, nivolumab may be more effective than regorafenib in nonprogressors (20). Research

reported that following sorafenib failure, nivolumab treatment is associated with improved OS (overall survival) and ORR compared with regorafenib treatment (21). Nivolumab plus ipilimumab was evaluated in patients with advanced HCC pretreated with sorafenib. The ORR was 31%, disease control rate (DCR) was 49% and a median duration of response was 17 months (22). NCCN recommends nivolumab as a subsequent therapy following disease progression in patients with CPA (Child-Pugh class A) or CPB (Child-Pugh class B) disease (a category 2A recommendation) (23). There are several other ongoing trials of combinations with nivolumab (Table I).

Pembrolizumab. Pembrolizumab (Keytruda), produced by Merck & Co, is a strong and selective humanized monoclonal antibody of IgG 4/ κ isotype (24). Nivolumab and pembrolizumab were enhanced by the Food and Drug Administration (FDA) on September 22 2017 and November 10 2018, respectively, as second-line options for HCC therapy, based on the results of the CheckMate 040 phase I/II trial and the KEYNOTE-224 phase II trial (24). In the KEYNOTE-224 trial, when patients with advanced HCC exhibited progression or intolerance to sorafenib, they received 200 mg pembrolizumab every 3 weeks. The results demonstrated that pembrolizumab was tolerated and had an ORR of 17% and stable disease rate of 44%, which initiated phase III (25). The phase III trial (KEYNOTE-240, identifier: NCT02702401) was performed to assess the safety and efficacy of pembrolizumab (26). However, the KEYNOTE-240 trial did not reach its specified endpoints of improvement in overall response (OR) and progression-free survival (PFS) with pembrolizumab. The ORR of the pembrolizumab group was markedly higher compared with the placebo group (16.9% vs. 2.2%) (25,26). Regardless of the implications for the credibility of pembrolizumab as second-line monotherapy for advanced HCC compared with placebo, the OS and PFS have exhibited clinically significant improvements, including the data from the KEYNOTE-224 trial (24). Pembrolizumab plus lenvatinib was evaluated in a phase Ib trial, whereby patients with CPA disease did not have prior systemic therapy, and the ORR was 50% and the control rate was 93.3%, lenvatinib plus pembrolizumab is being evaluated in a phase III study (NCT: 03713593) (27,28). NCCN recommends pembrolizumab as subsequent therapy following disease progression in patients with CPA liver function only (a category 2B recommendation) (23). There are several other ongoing trials of combinations involving pembrolizumab (Table II).

PD-L1 receptor blockers

Atezolizumab. Atezolizumab (Tecentriq), created by Genentech, is a monoclonal antibody against PD-L1 (29). PD-L1 acts in immune system inhibition induced by disease by inducing the proliferation of antigen-specific CD8⁺ T cells and controlling the accumulation of exogenous antigen-specific T cells (29). Although atezolizumab has been approved in the United States as a second-line therapy for urothelial carcinoma (30), trials focusing on its effect on HCC are still ongoing. The breakthrough IMbrave150 study demonstrated that at the time of the primary analysis, the hazard ratio for death with atezolizumab (atezo) + bevacizumab (bev) was 0.58 compared with sorafenib. Furthermore, OS time at 12 months

Table I. Ongoing clinical trials combined with nivolumab as second-line treatment for hepatocellular carcinoma.

Drug(s)	Phase	State	Location(s)	ClinicalTrial.gov reference
Nivolumab + Ipilimumab	II	Not yet recruiting	China	NCT03510871
Pexa Vec + Nivolumab	I/II	Active, not recruiting	France	NCT03071094
Cabozantinib + Nivolumab	I	Active, not recruiting	United States	NCT03299946
Nivolumab + BMS-813160 or Nivolumab + BMS-986253	II	Recruiting	United States	NCT04123379
Regorafenib + Nivolumab	I/II	Not yet recruiting	Spain	NCT04170556
Nivolumab + TACE	II	Recruiting	Germany	NCT03572582
Abemaciclib + Nivolumab	II	Not yet recruiting	United States	NCT03781960
SF112 + Nivolumab	I	Active, not recruiting	United States	NCT03059147
Nivolumab + Ipilimumab	III	Recruiting	Multinational	NCT04039607
CC-122 + Nivolumab	I/II	Active, not recruiting	Multinational	NCT02859324
Galunisertib + Nivolumab	I/II	Active, not recruiting	Multinational	NCT02423343
Nivolumab + Sorafenib	II	Recruiting	United States	NCT03439891
APL-101 + Nivolumab	I/II	Recruiting	Australia	NCT03655613
BMS-986183 + Nivolumab	I/II	Terminated	Multinational	NCT02828124
Copanlisib + Nivolumab	I/II	Recruiting	Multinational	NCT03735628
Vorolanib + Nivolumab	I	Recruiting	United States	NCT03511222
DSP-7888 + Nivolumab	I/II	Recruiting	United States	NCT03311334
Nivolumab + Metformin and Nivolumab + Rosiglitazone	II	Not yet recruiting	United States	NCT04114136
ALT-803 + Nivolumab	II	Recruiting	Multinational	NCT03228667

Table II. Ongoing trials combined with pembrolizumab as second-line treatment for hepatocellular carcinoma.

Drug(s)	Phase	State	Location(s)	ClinicalTrial.gov reference
Lenvatinib + Pembrolizumab	I	Active, not recruiting	Multinational	NCT03006926
TACE + Pembrolizumab	I/II	Recruiting	United Kingdom	NCT03397654
Regorafenib + Pembrolizumab	I	Recruiting	Multinational	NCT03347292
Sorafenib tosylate + Pembrolizumab	I/II	Recruiting	United States	NCT03211416
Lenvatinib + Pembrolizumab vs. Envatinib + Placebo	III	Recruiting	Multinational	NCT03713593
NKTR-214 + Pembrolizumab	I/II	Recruiting	United States	NCT03138889
Vorolanib + Pembrolizumab	I	Recruiting	United States	NCT03511222
DSP-7888 + Pembrolizumab	I/II	Recruiting	United States	NCT03311334
XmAb@22841 + Pembrolizumab	I	Recruiting	United States	NCT03849469
Pembrozilumab + Metformin and Pembrozilumab + Rosiglitazone	II	Not yet recruiting	United States	NCT04114136
ALT-803 + Pembrolizumab	II	Recruiting	Multinational	NCT03228667

was 67.2 and 54.6%, median PFS time was 6.8 and 4.3 months in the atezo+bev and sorafenib groups. Grade 3 or 4 adverse events occurred in 56.5% of 329 patients in the atezo+bev group and in 55.1% of 156 patients in the sorafenib group (31). Other high-grade toxic effects were rare, suggesting that atezo+bev lead to better OR and PFS outcomes compared with sorafenib in patients with unresectable HCC (31). Atezo+bev is likely to become the first-line drug for HCC, such as sorafenib. The primary endpoint of the study was improving PFS for atezo+bev. Arm F (in which patients were randomized

1:1 to atezo+bev or atezo) demonstrated that atezo and bev made separate contributions to the overall treatment effect. With longer follow-up, Arm A (in which patients received atezo+bev) demonstrated a sustained response to atezo+bev monotherapy, which together with tolerable safety demonstrates that atezo+bev has potential as a first-line treatment for unresectable HCC (32). There are ongoing trials (Table III).

Avelumab. Avelumab (Bavencio), a product of Merck KGaA and Pfizer, is also a PD-L1 receptor blocker. Data from a

Table III. Ongoing trials of the listed PD-L1 receptor blockers not included in second-line treatment for hepatocellular carcinoma.

Drug(s)	Phase	State	Location(s)	ClinicalTrial.gov reference
Atezolizumab + Bevacizumab	II	Not yet recruiting	China	NCT04180072
Atezolizumab + Bevacizumab vs. Active surveillance	III	Recruiting	Multinational	NCT04102098
Atezolizumab + Bevacizumab vs. Sorafenib	III	Recruiting	Multinational	NCT03434379
KY1044 + Atezolizumab	I/II	Recruiting	Multinational	NCT03829501
ALT-803 + Atezolizumab	II	Recruiting	United States	NCT03228667
FT500 + Atezolizumab	II	Recruiting	United States	NCT03841110
Durvalumab + Tremelimumab	II	Recruiting	United States	NCT03638141
Durvalumab alone or combined with Bevacizumab	III	Recruiting	Multinational	NCT03847428
Tivozanib + Durvalumab	I/II	Recruiting	United States	NCT03970616
Durvalumab + Guadecitabine	I	Recruiting	United States	NCT03257761
Cabozantinib + Durvalumab	I	Recruiting	United States	NCT03539822
Regorafenib + Avelumab	I/II	Recruiting	France	NCT03475953
ALT-803 + Avelumab	II	Recruiting	United States	NCT03228667
Cemiplimab + Platinum doublet	II	Recruiting	United States	NCT03916627

phase Ib trial of first-line avelumab+axitinib in patients with advanced HCC (NCT03289533) demonstrated that 15 (68.2%) and 16 (72.7%) patients met RECIST and mRECIST criteria, respectively, with ORRs of 13.6 and 31.8%, respectively. The preliminary safety of avelumab+axitinib in HCC has been established, and both avelumab and axitinib are known to be safe when administered as monotherapy (33). These results suggest antineoplastic activity in HCC (Table III).

Durvalumab. Durvalumab (Imfinzi) is a humanized monoclonal antibody against PD-L1 protein developed by AstraZeneca (34). Durvalumab 10 mg/kg Q2W has been demonstrated to exert antineoplastic activity and OS, with a tolerable safety profile in a liver cancer population; the ORR was 10.0%, with a median OS time of 13.2 months (35). A phase I/II study of durvalumab and tremelimumab in patients with unresectable HCC (NCT02519348) demonstrated no unexpected safety outcomes. The combination resulted in a durable ORR of 18% and clinical activity was mainly observed in patients without concomitant HBV or HCV infection, although interpretation of the results was limited by the small subset of 40 patients (36). Combined ICI therapy with tremelimumab and durvalumab in patients with HCC (NCT02821754) was well tolerated and exhibited productive activity (37). A randomized, multicenter phase III study of durvalumab and tremelimumab as first-line treatment in patients with unresectable HCC (NCT03298451) is still ongoing. In a study of ramucirumab and durvalumab treatment of metastatic NSCLC, gastric/gastroesophageal junction (G/GJ) adenocarcinoma and HCC (NCT02572687) exhibited no unexpected toxicity, and the combination exerted antitumor activity, with a durable ORR of 11% (38). Results in patients with high-PD-L1 HCC warrant further assessment (Table III).

Cemiplimab. Cemiplimab (Libtayo), produced by Sanofi and Regeneron, is an intravenous immunotherapy targeting the PD-1 pathway that helps the immune system fight cancer cells (39). In the phase I trial (NCT02383212), patients with

advanced or metastatic HCC using cemiplimab 3 mg/kg Q2W produced an ORR of 19.2%, the durable disease control rate was 42.3% and the median observation time to response was 1.9 months (40). The results indicate a meaningful therapeutic effect in advanced or metastatic HCC, and the safety is similar to other PD-1/PD-L1 blockers (Table III).

3. Listed drugs in China

Recently, several countries, including China, have focused research on PD-1/PD-L1 inhibitors to develop novel drugs (41-45). Chinese companies, such as Junshi Bioscience, Xinda Bioscience and Hengrui Medicine aim to compete with Bristol-Myers Squibb, Merck & Co., Inc. and other famous pharmaceutical enterprises. Although there is a long process from research to improvement in clinical outcomes, Chinese pharmaceutical companies hope to see patients benefit from their efforts.

On June 15, 2018, the China CFDA approved the listing of the nivolumab injection, which was the first PD-1 receptor blocker to be approved for marketing in China. Pembrolizumab entered the Chinese market shortly afterwards as a second-line option for HCC therapy, along with nivolumab. To advance the development of tumor immunotherapy, Chinese pharmaceutical companies have also independently developed new PD-1/PD-L1 inhibitors, including toripalimab, sintilimab, camrelizumab and tislelizumab (41). All the listed drugs in China have their own limited indications, and their effectiveness and safety in HCC is still under investigation in clinical trials (Table IV).

Toripalimab. Toripalimab is a domestic novel recombinant human anti-PD-1 monoclonal antibody, which is the first self-developed PD-1 inhibitor in China. Toripalimab was approved by the National Medical Products Administration in December 2018 to treat unresectable or metastatic malignant melanoma that failed to respond to prior systemic treatment (42). There are other clinical trials of toripalimab in

Table IV. Listed drugs produced in China under the clinical trails for hepatocellular carcinoma.

Drug(s)	Study title	Phase	State	Sponsor	ClinicalTrial.gov reference
Toripalimab	TAI + Toripalimab	II	Recruiting	Sun Yat-sen University	NCT03851939
	HAIC + Lenvatinib + Toripalimab	II	Recruiting	Shi Ming	NCT04044313
	Systemic chemotherapy + Lenvatinib and Toripalimab	II	Recruiting	Sun Yat-sen University	NCT04170179
	Sorafenib + Toripalimab	I/II	Not yet recruiting	Sichuan University	NCT04069949
Sintilimab	Anlotinib + Sintilimab	II	Recruiting	The First Affiliated Hospital with Nanjing Medical University	NCT04052152
	Sintilimab + IBI305	I	Recruiting	Chinese Academy of Medical Sciences	NCT04072679
	Sintilimab + Lenvatinib	II	Not yet recruiting	Baocai Xing	NCT04042805
	Sintilimab + IBI305 vs. Sorafenib	II/III	Recruiting	Innovent Biologics (Suzhou) Co., Ltd.	NCT03794440
Camrelizumab	Camrelizumab + Apatinib	I/II	Recruiting	Zhejiang University	NCT04035876
	HAIC + Camrelizumab	II	Recruiting	Sun Yat-sen University	NCT04191889
Tislelizumab	Regorafenib + Tislelizumab	II	Not yet recruiting	National Taiwan University Hospital	NCT04183088
	Sitravatinib	I/II	Recruiting	BeiGene	NCT03941873

HCC (42,43), including a multicenter phase III clinical study of postoperative high-risk HCC resection, with toripalimab as adjunctive therapy, the main purpose of this study was to determine the clinical efficacy of JS001 as postoperative adjuvant therapy in patients with advanced HCC compared with placebo, and to evaluate the safety and tolerance of JS001 (43).

Camrelizumab. At the end of 2018, the FDA and CFDA approved camrelizumab in combination with apatinib for first-line treatment of advanced liver cancer based on the results of a multicenter phase III study (NCT03764293) (43). At the ASCO meeting in 2019, Shukui Qin reported the results of a multicenter phase II study of camrelizumab combined with FOLFOX-4 or GEMOX as first-line treatment for advanced HCC or cholangiocarcinoma (BTC). The ORR of the 34 patients in the HCC group was 26.5% and the DCR was 79.4%, not up to median overall survival. The incidence of level 3 and above treatment-related adverse events was 85.3% in the HCC group, and grade 3 and above immune-related adverse events accounted for only 5.9%, suggesting that the combination of the camrelizumab monoclonal antibody with FOLFOX4 or GEMOX chemotherapy is well tolerated. This combination is expected to be effective for advanced HCC (44). A randomized, controlled, multicenter phase III study of camrelizumab combined with FOLFOX4 systemic chemotherapy for advanced HCC is being carried out (NCT 03605706) (44).

Tislelizumab. Tislelizumab has attracted great attention due to its high ORR in classical Hodgkin's lymphoma therapy (45). Experimental data from an international multicenter phase IA/IB clinical study of tislelizumab treatment for advanced solid tumor demonstrated that the ORR among 50 patients

with liver cancer was 12.2% and the DCR was 51% (46). An international multicenter phase II clinical trial, RATIONALE 301, comparing tislelizumab with sorafenib as the first-line treatment of advanced liver cancer is ongoing.

4. Influencing factors

PD-1 and PD-L1 expression, biomarkers of inflammation, and inflammatory genes, including CD274, CD8A, LAG3 and STAT1, have been developed with improved survival and response (47). Biomarkers have been reported to be associated with clinical outcomes (48). High PD-1 expression may indicate that T cells have been depleted in the tumor microenvironment (TME), which can help identify which type of patient will benefit from ICI therapy by inhibiting the PD-1/PD-L1 signal axis (39). Markers of systemic inflammation, such as elevated neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and α -fetoprotein are associated with poor prognosis in HCC (40).

Recent evidence suggest that when cells gradually evolve into malignant tumors, PD-L1 expression increases and the interaction between PD-1 and PD-L1 inhibits the self-reactive T cells, resulting in the over balance of PD-L1, PD-L2 and PD-1 (49). It has been demonstrated that androgen (AR) receptor can inhibit PD-L1 expression in HCC cells, and AR transcriptionally represses PD-L1 by binding to its promoter. In human clinical HCC samples, AR is negatively associated with PD-L1 expression (50). Thus, overexpression of AR weakens the effect of PD-L1 inhibitors *in vivo*.

Previous studies have demonstrated that EGFR signaling also regulates host antitumor immunity, including driving PD-L1 expression (51-53). In non-small cell lung cancer (NSCLC), the role of EGFR signaling on PD-L1 has made

a breakthrough. Compared with NSCLC cell lines with wild-type EGFR, PD-L1 expression is significantly higher in cell lines with mutant EGFR (54). Using EGFR-TKIs (gefitinib or erlotinib) to inhibit EGFR can decrease PD-L1 expression in NSCLC cell lines with mutant EGFR (55). Increasing evidence suggest that inhibiting EGFR can modulate the TME, which will optimize the antitumor activity of immunotherapy and increase the number of patients who benefit from PD-1/PD-L1 inhibitors (51-55).

5. Discussion

Nivolumab and pembrolizumab have been brought into guidelines due to their exact efficacy (11). PD-1 and PD-L1 expression, biomarkers of inflammation, inflammatory genes, AR and EGFR signaling have clear evidence of the impact on PD-1/PD-L1 clinical outcomes (47-55). The reason why cemiplimab, atezolizumab, avelumab, durvalumab have not been included in the guidelines for the treatment of HCC is that their efficacy and safety is not completely certain, and several trials are still ongoing (29-40). Nivolumab as a first-line treatment option compared with sorafenib is still under research, and nivolumab may become first-line treatment if the result is positive (12-23); atezo+bev has potential as a first-line treatment for unresectable HCC; both avelumab and axitinib are known to be safe when administered as monotherapy; cemiplimab and durvalumab have also demonstrated effectiveness in ORR (30,33,35,37,40). With an increase in the number of clinical trials, cemiplimab, atezolizumab, avelumab and durvalumab may be added to the guidelines. The breakthrough of the IMbrave150 trial offers the best pick-me-up to the development and application of PD-1/PD-L1 inhibitors (31).

Recent Chinese effort on PD-1 and PD-L1 blockers has proved useful, including toripalimab, sintilimab, camrelizumab and tislelizumab (42-45). They are listed in China with their specific indications, and their efficacy and safety in patients with HCC is under research. The results have demonstrated that the combination of camrelizumab with FOLFOX4 or GEMOX chemotherapy is well tolerated, and this combination is expected to be effective for advanced HCC (43,44). In addition, tislelizumab has exhibited effectiveness in ORR (45). In each willingness to pay (WTP) threshold among different countries, United States has a high WTP, which is 10,000~150,000/quality-adjusted life year, while the PD-1/PD-L1 inhibitors produced by China are more cost-effective (56).

6. Conclusions

The present review introduces eight drugs targeting PD-1 and PD-L1 developed in the United States, France, England and China, two of which (nivolumab and pembrolizumab) have been recommended as second-line options for patients with HCC by the NCCN clinical practice guidelines. ICIs targeting PD-1/PD-L1 have notably improved the symptoms of several patients with different malignant tumors. However, treatment is associated with typically transient immune-related adverse events (irAEs), which are severe or even deadly (57-59). Rapidly detecting these side effects and efficiently activating systemic immunosuppression can improve outcomes, without

affecting the efficacy of ICIs (57). A common and early irAE associated with ICIs is dermatologic toxicity, which can lead to dermatologic/mucosal toxicity, and oral mucositis and/or dry mouth symptoms have been observed following treatment with PD-1/PD-L1 (58). Other common irAEs include diarrhea and effects on the adrenal, pituitary and thyroid glands, which are difficult to identify due to the atypical symptoms, including fatigue, headache and nausea. Less frequent irAEs are observed in the lung, eye, kidney and pancreas (59). Meta-analyses of treatment-related adverse events in 2018 and 2019 (60,61) demonstrated that the most common all-grade adverse events were fatigue, diarrhea and pruritus. The most common grade 3 or higher adverse events were anemia, fatigue and increased aspartate aminotransferase. Hypothyroidism (6.07%) and hyperthyroidism (2.82%) were the most frequent all-grade endocrine irAEs. In addition, the rates of hypothyroidism pneumonitis, colitis and hypophysitis were higher in the presence of anti-PD-1 drugs compared with standard treatment. Among the general adverse events associated with immune activation, only the incidence of rash increased, whereas the incidence of diarrhea and fatigue were similar to the control group (60,61).

With the rapid development of molecular immunology and molecular biology, immunotherapy has emerged as a novel strategy with some promising results. However, it is not without limitations. The influencing factors, such as AR, require further investigation to improve the clinical outcomes, along with the suitable combination therapy for elevating response rate. In addition, more biomarkers are required to accurately predict efficacy, and it is essential to overcome immunotherapy resistance.

Pharmacists can easily collect PD-1/PD-L1-related data to provide a reference for clinicians, and the available data indicates that the development of PD-1/PD-L1 inhibitors to treat HCC will provide more options for combination therapy, and improve outcomes in patients who do not respond to first-line treatment. Publication of the results of ongoing clinical trials of PD-1/PD-L1 inhibitors is believed to provide more data and insight for the effective treatment of HCC.

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Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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