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Immunotherapy for hepatocellular carcinoma: current status and future perspectives

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ABSTRACT

The discovery of the immune checkpoint mechanism has contributed greatly to recent advances in cancer treatment. The anticytotoxic T lymphocyte-associated protein 4 antibody ipilimumab was first approved as a therapeutic drug for malignant melanoma in the USA in 2011; since then, antiprogrammed cell death 1 (PD-1) antibody and antiprogrammed death-ligand 1 (PD-L1) antibody have also been approved and clinically introduced and are indicated for the treatment of various cancers. Numerous clinical studies are now underway to evaluate the efficacy of immune checkpoint inhibitors for patients with many kinds of cancer, including hepatocellular carcinoma (HCC), and the outcomes of these trials are highly anticipated. Synergic effects of immune checkpoint inhibitors used in combination with molecular targeted agents or local therapy have also been suggested, resulting in expectations regarding the use of these drugs in combination with existing standard treatment methods for HCC. Thus, the treatment of HCC is now entering an age of significant innovation triggered by the clinical introduction of immune checkpoint inhibitors.

INTRODUCTION

Recent studies have revealed that cancer creates a special environment, known as the 'tumour microenvironment', to escape from the immunological surveillance system and continues to grow under this environment while suppressing the activation of immunocompetent cells (immune suppression). Such immune suppression has been reported to involve multiple mechanisms; among these mechanisms, the discovery of the immune checkpoint mechanism and its related molecules has contributed greatly to advances in cancer treatment. Of the various molecules involved in the immune checkpoint, programmed death-ligand 1 (PD-L1) (found on the surface of cancer cells and stromal cells) and programmed cell death 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) (found on the surface of T cells) have been shown to play particularly important roles in the suppression of T cell activation by cancer cells. The clinical development of monoclonal antibodies (immune checkpoint inhibitors) intended to inhibit the function of these molecules in several types of cancer is now underway. A strong efficacy of such monoclonal antibodies against specific types of cancer known to have a particularly high immunogenicity (eg, malignant melanoma) has been reported to date. In 2011, ipilimumab (an anti-CTLA-4 antibody) was approved for the treatment of malignant melanoma in the USA, followed by the approval and clinical introduction of two anti-PD-1 antibodies (nivolumab and pembrolizumab) and two anti-PD-L1 antibodies (atezolizumab and avelumab) for the treatment of several types of cancer.

Active efforts have also been made to develop similar therapies for hepatocellular carcinoma (HCC). At present, many phase III trials are underway, and both basic and clinical researchers are waiting for the outcomes of these trials with high expectations (tables 1 and 2). Among these drugs, nivolumab is at the most advanced stage of clinical development, and the outcome of its phase III trial will soon be available (as of September 2018).

MONOTHERAPY WITH AN IMMUNE CHECKPOINT INHIBITOR

The PD-L1/PD-1 pathway that constitutes the immune checkpoint mechanism is now considered to serve as the most important target of treatment, and current efforts to develop an immune checkpoint inhibitor monotherapy for HCC are focusing on anti-PD-1 antibodies or anti-PD-L1 antibodies.

Nivolumab

A phase I/II trial (CheckMate 040) for the anti-PD-1 antibody nivolumab against HCC has been completed.[1] In this trial, patients who were sorafenib naive, sorafenib intolerant or sorafenib refractory were treated with nivolumab at dose levels of 0.1–10 mg/kg once every 2 weeks (dose-escalating cohort) or at a dose level of 3 mg/kg once every 2 weeks (expansion cohort). Such treatment in 262 patients yielded a manageable

Table 1 Immune checkpoint inhibitors under evaluation in main clinical trials for hepatocellular carcinoma (as of September 2018)

Target	Immune checkpoint blocker (code name)	Trade name	IgG class	Company
PD-1	Nivolumab (ONO-4538, MDX-1106, BMS-936558)	OPDIVO	IgG4, human	Bristol-Meyers Squibb/Ono
	Pembrolizumab (MK-3475)	KEYTRUDA	IgG4, humanised	Merck Sharp and Dohme
	Tislelizumab (BGB-A317)		IgG4, humanised	BeiGene Boehringer Ingelheim
	Camrelizumab (SHR-1210)		IgG4, humanised	Jiangsu HengRui and Incyte
	Spartalizumab (PDR001)		IgG4, humanised	Novartis
PD-L1	Durvalumab (MEDI4736)	IMFINZI	IgG1*k*, human	Medimmune/AstraZeneca
	Atezolizumab (MPDL3280A)	TECENTRIQ	IgG1, humanised	Roche
	Avelumab (MSB0010718C)	BAVENCIO	IgG1, human	Merck KGaA, Pfizer and Eli Lilly
CTLA-4	Tremelimumab (CP 675206)		IgG2, human	Medimmune/AstraZeneca
	Ipilimumab (BMS-734016, MDX-010)	YERVOY	IgG1, human	Bristol-Meyers Squibb/Ono

CTLA-4, anticytotoxic T lymphocyte-associated protein 4;Ig, immunoglobulin;PD-1, programmed cell death 1;PD-L1, programmed death-ligand 1.

safety profile and a promising efficacy (dose escalation cohort: response rate of 15%, median survival period of 15 months; expansion cohort: response rate of 20%, 9-month survival rate of 74%). Based on the results of this trial, the FDA accelerated the approval of nivolumab for the treatment of patients with HCC who had been previously treated with sorafenib in the USA.

Building on the favourable results of this phase I/II trial, two phase III trials are now underway. In one of these trials (NCT02576509, CheckMate-459), patients

Table 2 Main trials for immune checkpoint inhibitors under evaluation in patients with hepatocellular carcinoma (as of September 2018)

Lines of therapy	Treatments	Primary endpoint	Study start	Estimated enrollment	ClinicalTrials.gov (study name)
First-line therapy					
	Nivolumab vs Sorafenib	OS	November 2015	726	NCT02576509 (CheckMate-459)
	Tislelizumab (BGB-A317) versus sorafenib	OS	December 2017	660	NCT03412773
	Durvalumab versus durvalumab+tremelimumab (regimen 1) versus durvalumab+tremelimumab (regimen 2) versus sorafenib	OS	October 2017	1200	NCT03298451 (HIMALAYA)
	Atezolizumab+bevacizumab versus sorafenib	OS	March 2018	480	NCT03434379 (IMbrave150)
Second-line therapy					
	Pembrolizumab versus placebo	PFS OS	May 2016	408	NCT02702401 (KEYNOTE-240)
	Pembrolizumab versus placebo	OS	April 2017	330	NCT03062358 (KEYNOTE-394)
Adjuvant therapy					
	Nivolumab versus placebo	PFS	December 2017	530	NCT03383458 (CheckMate 9DX)

OS, overall survival; PFS, progression-free survival.

were randomised to two arms, nivolumab or sorafenib, for comparisons of overall survival and progression-free survival.[2] The second phase III trial (CheckMate 9DX, NCT03383458) was designed to evaluate the efficacy of nivolumab as an adjuvant therapy after surgical resection or ablation therapy. This trial allocated patients with a high risk of recurrence to two groups (a nivolumab group and a placebo group); treatment will be continued until recurrence to compare the recurrence-free survival period as the primary endpoint. At present (September 2018), this is the only phase III trial using an immune checkpoint inhibitor as an adjuvant therapy in patients with HCC.

Pembrolizumab

In contrast to nivolumab, which is presently being developed as first-line treatment, pembrolizumab (another anti-PD-1 antibody) is being developed primarily as a second-line treatment. In a phase II trial for this drug (KEYNOTE-224, NCT02702414), pembrolizumab (200 mg) was administered at intervals of 3 weeks to sorafenib-refractory or sorafenib-intolerant patients (Cohort 1) and patients without a history of previous systemic treatment (Cohort 2).[3] The interim results for 104 sorafenib-refractory or sorafenib-intolerant patients were reported at a meeting of the American Society of Clinical Oncology (ASCO) in 2018, with promising results as a second-line treatment (response rate of 18%, median survival period of 12.9 months). Furthermore, in a phase II trial conducted at a single institute (University of Miami), results approximately equal to those above were obtained in sorafenib-refractory or sorafenib-intolerant patients or patients who refused sorafenib treatment (response rate of 33%, median survival period of 14 months).

Meanwhile, two ongoing phase III trials were started approximately simultaneously with the above-mentioned trials. One of them is a global phase III trial allocating patients to a pembrolizumab group or a placebo group (KEYNOTE-240, NCT02702401).[4] The primary endpoints will be progression-free survival and overall survival. Another phase III trial involving five Asian countries has set survival as the primary endpoint (KEYNOTE-394, NCT03062358). Both trials involve patients with a history of prior systemic chemotherapy.

Tislelizumab

Tislelizumab (BGB-A317) is an anti-PD-1 antibody being developed by BeiGene. After its safety was confirmed in a phase I trial involving 61 patients with solid cancers, including HCC, a global phase III trial was started in December 2017; patients were allocated to two groups, tislelizumab or sorafenib, as a first-line treatment.[5] This trial has set survival as the primary endpoint and is designed to verify the non-inferiority of tislelizumab, compared with sorafenib (NCT03412773).

Camrelizumab

Camrelizumab (SHR-1210) is an anti-PD-1 antibody being developed jointly by Incyte and Jiangsu HengRui. A phase I trial was performed in 58 patients with solid cancers (including HCC), with one of the three patients with HCC exhibiting a response.[6] At present, a phase II/III trial is underway in China involving patients who failed to respond or were intolerant to prior systemic treatment (NCT02989922). According to the interim results of the phase II part reported at a meeting of the European Society for Medical Oncology (ESMO) in 2018, the response rate was 13.8% (30/217) and 6-month overall survival rate was 74.7%. Although two patients (0.9%) experienced grade 5 treatment-related adverse events, camrelizumab seemed to have acceptable toxicities profile in pretreated patients with advanced HCC.[7]

Durvalumab

Although all the drugs presented above are anti-PD-1 antibodies, durvalumab is an anti-PD-L1 antibody. This is the only anti-PD-L1 antibody for which a phase III trial examining the use of such a drug for HCC monotherapy is underway (as of September 2018). A phase I/II trial of durvalumab monotherapy for solid cancers, including HCC, has been completed, with a 10% response rate and a median survival time of 13.2 months observed for a cohort of 40 patients with HCC.[8] Durvalumab plus tremelimumab (an anti-CTLA-4 antibody) combination therapy has also been developed, and a phase III trial is now underway (presented in the next section) to evaluate the efficacy of both durvalumab monotherapy and durvalumab plus tremelimumab combination therapy.[9]

Tremelimumab

Tremelimumab is an anti-CTLA-4 antibody, which is the only anti-CTLA-4 antibody for which a phase III trial examining the use of such a drug for HCC monotherapy is underway (as of September 2018). A clinical trial of tremelimumab monotherapy for patients with HCC and chronic hepatitis C virus infection has been conducted.[10] Among the 21 enrolled patients, partial response rate was 17.6% and a median time to progression was 6.48 months. The treatment was overall well tolerated with some patients experiencing grade 3–4 toxicities such as transient elevation of transaminases. The study also showed a significant drop in viral load that warrant further investigation in large clinical trials.

COMBINATION TREATMENT

It has been suggested that the anticancer response to PD-1/PD-L1 inhibitors might be enhanced if these drugs were to be used in combination with other treatments. In this section, we present several combined therapies that are expected to be effective against HCC.

Combination with other immune checkpoint inhibitors (anti-CTLA-4 antibodies)

Anti-CTLA-4 antibodies bind to CTLA-4 molecules expressed on the surface of cytotoxic T cells and regulatory T cells (Treg cells) and thus reinforce the antitumour activity of cytotoxic T cells, thereby enhancing the immune

responses induced by PD-1/PD-L1 inhibitors. In patients with malignant melanoma, a phase III trial designed to compare nivolumab monotherapy, ipilimumab (an anti-CTLA-4 antibody) monotherapy and nivolumab+ipilimumab combination treatment has been performed and demonstrated that the progression-free survivals were 6.9 months, 2.9 months and 11.5 months, respectively, and that the median survivals were 37.6 months, 19.9 months and not reached, respectively, with significantly better results reported for the combination treatment, compared with ipilimumab monotherapy, in terms of both progression-free survival and median survival .[11] Currently, this combined therapy is also being evaluated in clinical trials for other types of cancer in addition to HCC.

Durvalumab + Tremelimumab

Combination treatment with the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab is also being assessed in a phase I/II trial for patients with HCC. The phase I study enrolled 40 patients and had a response rate of 25%,[12] suggesting that this combined therapy might be more effective than durvalumab monotherapy. The study also showed that the combination had manageable toxicity profile: most common grade 3 or greater treatment-related adverse event was asymptomatic increased aspartate aminotransferase (10%).

At present, a global phase III trial is underway to compare the efficacy of different regimens as a first-line treatment; the four arms consist of durvalumab monotherapy, two types of durvalumab+tremelimumab combination therapies (regimens 1 and 2) and sorafenib monotherapy (NCT03298451).[9]

Nivolumab + Ipilimumab

In the CheckMate 040 trial, the combination of nivolumab plus ipilimumab is being evaluated in addition to nivolumab alone (NCT01658878), and the results are eagerly awaited. Now, two clinical studies examining the combination of nivolumab plus ipilimumab as a neoadjuvant therapy are ongoing. One of these studies is a randomised phase II trial in the USA comparing nivolumab monotherapy with nivolumab plus ipilimumab combination therapy (NCT03222076). The other is a phase II trial planned in Taiwan to evaluate the combination therapy alone (NCT03510871).

Combination with molecular targeted agents

Immune checkpoint inhibitors are expected to exert synergistic effects when combined with chemotherapeutic agents or molecular targeted agents. Because several antiangiogenic inhibitors have been shown to be useful for the treatment of HCC, the combination of immune checkpoint inhibitors with these antiangiogenic inhibitors is now very much anticipated, and some promising results have already been reported.

Atezolizumab + Bevacizumab

A phase I trial of combined atezolizumab (anti-PD-L1 inhibitor) plus bevacizumab (anti-VEGF antibody) therapy is now underway involving patients with HCC.[13] According to the interim results reported at a meeting of the ESMO in 2018, the response rate at the presentation was 32% (23/73) in the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. Responses were durable, with 52% lasting for 6 months or more and 26% lasting 12 months or more. Grade 3–4 treatment-related adverse events were seen in 27% (28/103), most commonly hypertension (10%, 10/103). Although two patients (2%) experienced grade 5 treatment-related adverse events, the combination was generally tolerable with a manageable safety profile. A global phase III trial for this therapy as a first-line treatment was started to compare the survival outcomes between combined therapy and sorafenib monotherapy (NCT03434379).[14]

Pembrolizumab + Lenvatinib

Lenvatinib is a multikinase inhibitor targeting various signal receptors such as the three main vascular endothelial growth factor receptors (VEGFR1, 2 and 3) as well as fibroblast growth factor receptors (FGFR) 1, 2, 3 and 4, platelet-derived growth factor receptor (PDGFR) alpha, c-Kit and the RET proto-oncogene. The non-inferiority of this drug to sorafenib was demonstrated in a phase III trial for patients with HCC, allowing the drug to be positioned as a new standard for first-line treatment. In preclinical studies, this drug has been shown to enhance the activity of anti-PD-1 antibodies, and clinical studies examining lenvatinib plus pembrolizumab combination therapy for various types of cancer have been started. A phase I trial for this therapy is also underway in patients with HCC. According to results reported preliminarily at the ASCO meeting in 2018, the response rate in the modified RECIST criteria among the 26 patients who were evaluated was 42% and the median progression-free survival period was 9.69 months.[15] Although some patients showed grade 3 or higher treatment-related adverse events, the most common ones were elevation of alanine aminotransferase and hypertension (17% each); the therapy was generally well tolerated.

SHR-1210 + Apatinib

SHR-1210 is an anti-PD-1 antibody, and a phase I trial on treatment with this drug in combination with apatinib (a tyrosine kinase inhibitor selectively acting on VEGFR2) was reported at the ASCO meeting in 2018.[16] The trial enrolled 18 patients with HCC and a response rate of 38.9% and a median progression-free survival of 7.2 months were reported. The adverse events were manageable, while only one patient discontinued treatment due to treatment-related grade 3 hyperbilirubinaemia.

Others

At present, numerous early stage clinical studies are underway for the treatment of HCC with various combinations of PD-1 pathway inhibitors and antiangiogenic inhibitors including nivolumab plus lenvatinib (NCT03418922), nivolumab plus cabozantinib (NCT03299946), nivolumab

plus bevacizumab (NCT03382886), pembrolizumab plus regorafenib (NCT03347292), pembrolizumab plus sorafenib (NCT03211416), PDR001 (spartalizumab) plus sorafenib (NCT02988440), avelumab plus axitinib (NCT03289533), durvalumab plus ramucirumab (NCT02572687) and so on. Close attention is now being paid to trends in this field.

Combination with local therapy

Local therapy for cancer is expected to affect the tumour microenvironment and to reinforce the efficacy of immune checkpoint inhibitors. In addition, it is expected to enhance therapeutic efficacy by stimulating the release of tumour-associated antigens and neoantigens from cancer cells into the blood. Furthermore, the combination of radiotherapy with chemotherapeutic agents is expected to increase neoantigen release through a DNA-disturbing activity, possibly resulting in a higher efficacy of immune checkpoint inhibitors, the induction of immunogenic cell death and the reinforcement of therapeutic efficacy through a decrease in immunosuppressive cells such as Treg cells and myeloid-derived suppressor cells. In patients with HCC, in particular, local therapy such as radiofrequency ablation (RFA) and transcatheter arterial chemoembolisation (TACE) has often been used as a standard therapy, and many clinical studies have been started with the expectation of synergistic effects when immune checkpoint inhibitors are combined with such local therapeutic approaches.

Nivolumab + TACE

A therapy combining nivolumab with TACE using drug-eluting beads (DEB-TACE) has started. In the USA, a phase I trial of this therapy is underway.[17] In this study, nivolumab is administered intravenously every 2 weeks at a dose level of 240 mg. The trial is designed to evaluate the safety of this therapy in various schedules (NCT03143270). In Germany, a phase II trial of this therapy has been started comparing two regimens in which TACE is applied repeatedly at 8-week intervals and nivolumab treatment is started either 1 day after TACE or 2 days after TACE (days 2–3) and subsequently repeated at intervals of 2 weeks. This trial was designed to evaluate efficacy by setting the response rate as the primary endpoint (NCT03572582).

Pembrolizumab + TACE

A study designed to evaluate treatment with pembrolizumab in combination with TACE using doxorubicin (60 mg) and gelatin sponges has been started in the UK as a phase I/II trial. In this trial, pembrolizumab (200 mg) treatment is started 30 or 45 days after TACE and is subsequently applied repeatedly at 3-week intervals; the study is designed to evaluate the safety and efficacy (progression-free survival rate for each 12-week period) of pembrolizumab plus TACE (NCT03397654).

Tremelimumab + RFA or TACE

A pilot study regarding the combination of tremelimumab with local therapy (RFA or TACE) has been conducted.[18] Tremelimumab was administered at 4-week intervals, and local therapy was applied on day 36. The trial enrolled 32 patients with HCC. No dose-limiting toxicities were observed. Of the 19 evaluable patients, five patients (26.3%) achieved confirmed partial responses outside of the areas treated with ablation or TACE. One patient was found to have tumour growth at 8 weeks after the start of treatment, but the tumour diminished rapidly thereafter. The median progression-free survival period was 7.4 months, and the median survival period was 12.3 months. Tumour biopsies revealed a significant increase in cytotoxic T cells after the administration of tremelimumab.

Others

Other than the studies mentioned above, the following clinical studies are now underway: a phase II trial of nivolumab therapy combined with radioembolisation using yttrium-90 (NCT03033446),[19] a phase II trial of combined durvalumab+tremelimumab+ radiotherapy (NCT03482102), a phase I/II trial of pembrolizumab therapy combined with local immunotherapy using the oncolytic viral preparation talimogene laherparepvec (NCT02509507)[20] and so on.

FUTURE PERSPECTIVE

Recently, sorafenib and several other molecular-targeted agents have demonstrated survival advantages in patients with advanced HCC. However, the prognosis of patients with HCC is still quite poor, and further efforts to develop new treatment methods are needed. At present, many large-scale clinical studies are being conducted on immune checkpoint inhibitors because this class of drug is considered to have the highest likelihood of improving the prognosis of patients with HCC.

On the other hand, there are many problems and issues to be resolved for the therapeutic use of immune checkpoint inhibitors. One such problem is the fact that this therapy is not effective in all patients. Biomarkers capable of predicting antitumour responses are needed. In patients with malignant melanoma, the expression of PD-L1 in tumour tissue and the expression of tumour-infiltrating lymphocytes are reportedly associated with the efficacy of this therapy. Such evaluations have not been sufficiently conducted for patients with HCC. It is also evident that various immune-related adverse events (not seen with existing molecular targeted agents or anticancer drugs) can develop, occasionally leading to a fatal outcome. So, it is also important to diagnose such adverse events precisely and to provide appropriate treatment at an appropriate time. At present, it is not easy to overcome these adverse events completely, and the development of biomarkers to predict their onset is needed. If patients with HCC who are more likely to benefit from this therapy can be selected by predicting the likelihood of responses and adverse events, this therapy could be applied more safely, thereby reducing not only the physical burdens

of individual patients but also the economic burdens of society.

Enthusiasm to develop new standard treatments for HCC has been increasing rapidly since the introduction of immune checkpoint inhibitors to this field. We hope that the further accumulation of knowledge regarding the immune biology of HCC will continue to enhance the development of more effective therapies for patients with HCC and to overcome the associated open issues.

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