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REVIEW

Immune checkpoint inhibitors in esophageal squamous cell carcinoma: progress and opportunities

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Abstract: Esophageal squamous cell carcinoma (ESCC) is one of the common malignant tumors in the world. More than half of patients with ESCC were detected in advanced or metastatic disease at the time of initial diagnosis and lost the opportunities of surgery. Currently, surgical resection, radiotherapy, and chemotherapy are most utilized in clinical practice, however, they are associated with limited survival benefits. Recognition of the limitation of traditional antitumor strategies prompt the development of new means to treat human cancer. In recent years, studies on immune checkpoint inhibitors (eg PD-1/PD-L1 inhibitors, CTLA-4 inhibitors, etc.) in ESCC have shown promising results. In addition, the combination of immune checkpoint inhibitor and traditional antitumor strategies for ESCC has caused extensive interest, and the results are encouraging. Previous analysis indicated that tumor cell PD-L1 expression, tumor mutation load (TMB), microsatellite instability-high status (MSI-H), and other biomarkers have relatively correlated with the efficacy of immunotherapy. This review explores the recent studies investigating checkpoint inhibitors in ESCC.

Keywords: esophageal squamous cell carcinoma (ESCC), immune checkpoint inhibitors, biomarkers, research progress

Background

Esophageal cancer is the eighth most common cancer in the world and is the sixth leading cause of cancer-related deaths.[1] There were 572,034 cases of new diagnosed esophageal cancer worldwide and 508,585 deaths were reported in 2018, which is hence a real global health challenge.[1] The major histological types of esophageal cancer are squamous cell carcinoma and adenocarcinoma, moreover, histological subtypes and cancer incidence are closely related to geographical distribution.[2] Although the esophageal adenocarcinoma incidence is increasing in Western countries, esophageal squamous cell carcinoma (ESCC) predominates in Asia countries, including China. Because the clinical symptoms of early esophageal cancer are obscure, more than half of the patients are in the advanced stage when they are detected.[3] In this population of patients, palliative treatment is of great significance. However, the prognosis of patients in advanced or metastatic esophageal cancer was associated with a limited survival benefit, in fact, overall survival (OS) rate of 5 years was less than 15%.[4,5] The National Comprehensive Cancer Network (NCCN) guidelines recommended cisplatin or oxaliplatin together with fluorouracil or capecitabine as first-line chemotherapy regimen for ESCC or the esophageal adenocarcinoma.[6] The addition of epirubicin, irinotecan, or taxanes are correlated with an added benefit, but the disease control rate (DCR) for the combination chemotherapy regimens are less than 50%, and the median OS is less than 11 months, in addition, the combined

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regimens are associated with severe poisonousness.[6,7] Therefore, other anticancer strategies are urgently needed to improve the prognosis of these patients. In the past few decades, numerous clinical trials on targeted therapies using gefitinib, erlotinib and cetuximab showed insignificant survival benefits.[8–10] Recently, It is worth noting that the successive discovery and further study of immune checkpoints, such as programmed death protein 1 (PD-1), programmed death protein 1 ligand (PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4), make immunotherapy served as the fourth antitumor strategies following surgery, radiotherapy and chemotherapy.[11–13] Currently, immunotherapy is under extensive investigation and this review generalizes the most recent studies of immune checkpoint inhibitors for ESCC.

The mechanism of immune checkpoint

Various of co-stimulatory and inhibitory molecules form a complicated signaling pathway and involved in regulating the human immune function.[14]

In these pathways, T lymphocytes play an important role in activating the immune system and against foreign pathogens as well as tumor cells. There are many immune checkpoints expressed on the surface of T lymphocytes, including programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4).

PD-1 belonging to the immunoglobin superfamily contains immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoreceptor tyrosine-based switch motif (ITSM).[15] Usually, PD-1 couples with its ligands PD-L1 and PD-L2 to restrain the function of T cells in the immune system, involved in preventing autoimmune reaction and excessive inflammation, thus, protect the normal cells.[16,17] Tumor-infiltrating T lymphocytes (TILs) upregulate PD-L1 expression in tumor cells by secreting interferon γ.[17,18] More than 40% of ESCC and 18% of esophageal adenocarcinoma are correlated with PD-L1 overexpression, and the prognosis of patients with PD-L1 overexpression is worse than those without PD-L1 overexpression in ESCC.[19,20] Tumor cells can inhibit the function of effector T cells, through the PD-1/PD-L1 pathway, and cause immune escape.[17,18]

CTLA-4, also known as a T-cell receptor, belongs to the immunoglobulin superfamily. Similar to the T-cell surface co-stimulatory protein CD28, CTLA-4 competes with CD28 in binding to antigen presenting cell surface ligands CD80 (B7-1) and CD86 (B7-2), moreover, the combining capacity of CTLA-4 is stronger than CD28. CD28 is involved in the activation, proliferation, and migration of T cells, while CTLA-4 is mainly served as a suppressor, resulting in immune inhibition.[21,22] For CD4+ helper T lymphocytes (Th), CTLA-4 combines with ligand B7 and decreases T cell differentiation, down-regulates the production of lymphocyte factors, thereby suppresses the cellular immune system and humoral immune system. Conversely, in CD4+ regulatory T lymphocytes (Tregs), CTLA-4 binding with B7 induces the overexpression of a variety of immunosuppressive factors, as a result, enhances the immunosuppressive effect of Tregs cells, and promotes the immune escape of tumor cells. In addition, CTLA-4 expressed on T cells also down-regulates CD80 and CD86, decreases the stimulation between T cells and antigen-presenting cells, thus blocks the activation of the immune system.[22,23]

Continuous discovery of tumor-related immune mechanisms has promoted the development of immune checkpoint inhibitors, which is being the most exciting cancer treatment currently.

The application of immune checkpoint inhibitors in ESCC

PD-1/PD-L1 immune pathway inhibitors

Tumor cell ligands including PD-L1 and PD-L2 bind to the PD-1 receptor on activated T lymphocytes, inhibit the antitumor effect of T cells and lead to tumor cells immune escape. PD-1 or PD-L1 antibodies are applied to prevent the combination of PD-1 with its corresponding ligands, so as to reduce the immunosuppressive effect on effector T cells, and promote the anti-tumor effect of the body's immune system. To date, PD-1/PD-L1 inhibitors, including nivolumab, pembrolizumab, JS001, SHR-1210, durvalumab and SHR-1316, mainly applied in ESCC (Table 1).

Nivolumab is a high-affinity, humanized IgG4 monoclonal PD-1 antibody.[24] ATTRACTION-01 trial is an open multicenter phase II clinical study focused on the safety and antitumor efficacy of nivolumab in esophageal cancer, there are 65 patients with advanced ESCC recruited, these patients were refractory or could not tolerate chemotherapy, the objective response rate (0RR) was 17.2%, including 3 patients achieved complete response (CR) and 8 patients were partial response (PR), and the median duration of response (DOR) was 11.17 months. The 1-, 1.5- and 2-year OS rates were 45.3%, 25.0% and 17.2%, respectively, with progressive-free survival (PFS) rates of 1-, 1.5- and 2-year of 10.3%, 8.6% and 8.6%, respectively; only 17 (26%) patients had grade 3–4 adverse events (AEs) and there were no treatment-related deaths.[25,26] This clinical trial shows that

Table 1 List of ongoing clinical studies with immune checkpoint therapies for ESCC or malignant tumors including ESCC

Checkpoint inhibitors	Tumor	Treatment	Line	Phase	Primary endpoint	NCT Number
PD-1 inhibitor	ESCC	Pembrolizumab + chemoradiation	Neoadj.	Ib	Safety	NCT03792347
PD-1 inhibitor	ESCC	Pembrolizumab + chemoradiation	Neoadj.	II	pCR rate	NCT02844075
PD-1 inhibitor	Esophageal or gastroesophageal cancer	Pembrolizumab + epacadostat	Neoadj.	II	Anti-tumor immune response、AE	NCT03592407
PD-1 inhibitor	Esophageal and gastric cancer	Pembrolizumab + chemoradiation	Neoadj.	II	pCR rate	NCT03064490
PD-1 inhibitor	ESCC	SHR-1210+ radiation	Neoadj.	II	pCR rate	NCT03200691
PD-1 inhibitor	ESCC	Pembrolizumab + chemoradiotherapy	Adj.	II	1-year RFS rate	NCT03322267
PD-L1 inhibitor	ESCC	Durvalumab vs placebo	Adj.	II	DFS	NCT02520453
PD-1 inhibitor	ESCC	SHR-1210+ apatinib + irinotecan/paclitaxel liposome + nedaplatin	1st	II	PFS	NCT03603756
PD-L1 inhibitor	ESCC	SHR-1316+ irinotecan liposome + fluorouracil	1st	II	PFS	NCT03732508
PD-1 inhibitor	Esophageal cancer	Pembrolizumab + Cisplatin +5-Fluorouracil vs Placebo + Cisplatin +5-Fluorouracil	1st	III	PFS、OS	NCT03189719
PD-1 inhibitor	Esophageal cancer	SHR-1210 + paclitaxel + cisplatin vs placebo + paclitaxel + cisplatin	1st	III	PFS、OS	NCT03691090
PD-1 inhibitor/CTLA-4 inhibitor	ESCC	Nivolumab + Fluorouracil + Cisplatin or Nivolumab + Ipilimumab vs Fluorouracil + Cisplatin	1st	III	OS、PFS	NCT03143153
PD-1 inhibitor/CTLA-4 inhibitor	ESCC	Nivolumab ± Ipilimumab	2nd	II	OS	NCT03416244
PD-1 inhibitor	ESCC	SHR-1210+ apatinib	2nd	II	ORR	NCT03736863
PD-1 inhibitor	ESCC	SHR-1210+ nimotuzumab	2nd	II	ORR	NCT03766178
PD-1 inhibitor	Esophageal cancer	Nivolumab vs docetaxel/paclitaxel	2nd	III	OS	NCT02569242
PD-1 inhibitor	Esophageal cancer	Pembrolizumab vs docetaxel/paclitaxel/irinotecan	2nd	III	OS	NCT02564263
PD-1 inhibitor	Esophageal cancer	SHR-1210 vs docetaxel/irinotecan	2nd	III	OS	NCT03099382
PD-1 inhibitor	Esophageal cancer	Pembrolizumab	Salvage	II	ORR	NCT02971956
PD-1 inhibitor	Esophageal cancer	Pembrolizumab + radiation	–	I	AE	NCT02642809
PD-1 inhibitor	Advanced malignancies (including esophageal cancer)	JS001	–	I	AE	NCT03474640
PD-L1 inhibitor	Advanced solid tumors (including esophageal cancer)	Durvalumab	–	I	AE	NCT01938612
PD-1 inhibitor	ESCC	Nivolumab + carboplatin/paclitaxel + radiation	–	I/II	Safety	NCT03278626
PD-1 inhibitor	Esophageal cancer	Nivolumab + palliative radiotherapy/definitive chemoradiotherapy/ neoadjuvant chemoradiotherapy	–	I/II	AE	NCT03544736
PD-1 inhibitor	ESCC	JS001	–	Ib/II	ORR	NCT02915432
PD-L1 inhibitor/CTLA-4 inhibitor	Metastatic squamous cell Cancer (including ESCC)	Durvalumab + tremelimumab + stereotactic body radiotherapy (SBRT)	–	I/II	DLT	NCT03212469

(*Continued*)

Table 1 (Continued).

Checkpoint inhibitors	Tumor	Treatment	Line	Phase	Primary endpoint	NCT Number
PD-L1 inhibitor/CTLA-4 inhibitor	Esophageal cancer	Durvalumab ± tremelimumab + chemotherapy	–	I/II	AE、DLT	NCT02735239
PD-1 inhibitor	ESCC	SHR-1210+ apatinib + radiation	–	II	AE	NCT03671265
PD-1 inhibitor	ESCC	SHR-1210+ radiation	–	II	AE	NCT03222440
PD-1 inhibitor	ESCC	SHR-1210+ radiation	–	II	Local control	NCT03187314
PD-L1 inhibitor	Esophageal cancer	Durvalumab	–	II	RFS	NCT02639065
PD-L1 inhibitor	Esophageal cancer	Durvalumab + chemoradiation	–	II	PFS	NCT03777813
PD-1 inhibitor/CTLA-4 inhibitor	Esophageal cancer	Nivolumab ± ipilimumab + chemoradiation	–	II	PFS	NCT03437200
PD-L1 inhibitor/CTLA-4 inhibitor	ESCC	Durvalumab + tremelimumab + chemoradiation	–	II	PFS	NCT03377400

Abbreviations: ESCC, esophageal squamous cell carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand1; CTLA-4, cytotoxic T-lymphocyte antigen 4; pCR, pathological complete response; AE, adverse events; RFS, recurrence-free survival; DFS, disease free survival; PFS, progression free survival; OS, overall survival; ORR, objective response rate; DLT, dose limiting toxicity.

nivolumab has a controllable safety and durable antitumor activity in advanced ESCC. Recently, the latest results of phase III clinical trial ATTRACTION-03 are as follows: Nivolumab exposed a remarkable extension in OS when compared with chemotherapy (docetaxel or paclitaxel) in unresectable advanced or recurrent esophageal cancer patients who were refractory to or intolerant of fluoropyrimidine and platinum-based combination therapy.[27] Several studies concentrated on the treatment of esophageal cancer with nivolumab are currently underway (Table 1).

Pembrolizumab, a strong affinity with PD-1, is a genetically engineered human IgG4-k monoclonal antibody. Pembrolizumab has shown significant antitumor activity and safety in patients with advanced malignancies. KEYNOTE-028 trial is a phase Ib clinical study; the 23 esophageal cancer patients with standard treatment failure enrolled were PD-L1 positive (PD-L1 combined positive score (CPS) ≥1, in which CPS meant that the number of PD-L1 staining cell divided by the total number of viable tumor cells and multiplied by 100), and 78% of patients were ESCC. With a median follow-up of 7 months, the ORR was 30% and the median DOR was 15 months, and the ORR was 28% in the subgroup of ESCC patients (5/18). The incidence of grade 3 treatment-related AEs was 17%. There is No grade 4 AEs or treatment-related deaths occurred.[28] However, a phase II KEYNOTE-180 trial of advanced/metastatic esophageal cancer further assessed the safety and antitumor activity of pembrolizumab. Among the 63 patients with ESCC, the ORR was 14.3%, the DCR was 40%, the median PFS was 2.1 months, and the median OS was 6.8 months. Only 12.4% of patients experienced grade 3–5 treatment-related AEs, and 1 patient died of pneumonitis.[29] Recently, in the global phase III KEYNOTE-181 trial, pembrolizumab compared with chemotherapy (paclitaxel, docetaxel, or irinotecan) as second-line therapy for advanced esophageal cancer were performed. In the subgroup with ESCC, median OS was 8.2 months with pembrolizumab and 7.1 months with chemotherapy (hazard ratio [HR] =0.78, P= 0.0095), with 12 months, 24 months -OS rates of 39% vs 25%, and 23% vs 12%, respectively, and PFS rates at 12 months at of 21% vs 7% respectively. In the PD-L1 CPS≥10 subgroup (n=220), median OS was 9.3 months with pembrolizumab, while median OS was 6.7 months with chemotherapy (HR=0.69, P= 0.0074). In the pembrolizumab group, the 12 months -PFS rate (21% vs 7%) and the OS rate at 12 months (43% vs 20%) were higher than the chemotherapy group. Compared with chemotherapy,

fewer patients with pembrolizumab had experienced drug-related AEs.[30] The results of this trial have brought hope to immune checkpoint inhibitors as a new second-line treatment for ESCC. In addition, there are still several clinical studies focusing on pembrolizumab as a first-line or second-line treatment for esophageal cancer (Table 1).

JS001 is a new recombinant humanized IgG4 monoclonal PD-1 antibody developed by China. In an open, multi-center phase Ib/II trial, 34 patients of metastatic ESCC were eligible for evaluated efficacy; 8 patients achieved PR, 14 patients achieved stable disease (SD). In the 10 patients of PD-L1 positive (PD-L1 CPS ≥1), only 2 (20%) people were PR; and in the 24 patients of negative PD-L1 (PD-L1 CPS < 1), 6 (25%) people achieved PR.[31] The preliminary results showed that the clinical efficacy of JS001 was not related to PD-L1 expression and this study is still ongoing. Other studies include a phase I trial of JS001 for patients with advanced esophageal cancers (NCT03474640).

SHR-1210 is a humanized IgG4-kappa monoclonal PD-1 antibody with high affinity and selectivity developed by China. MoH et al reported that SHR-1210 had durable anti-tumor activity and controllable safety.[32] In a phase I clinical study of advanced ESCC that is refractory or intolerant to chemotherapy, SHR-1210 was administered to 30 patients, the results revealed an ORR of 33.3%, DCR of 56.7%, and median PFS of 3.6 months. However, 23 (76.7%) patients developed reactive capillary hemangioma and 3 (10%) patients developed grade 3 treatment-related AEs (2 pneumonitis and 1 increased cardiac troponin I).[33] The incidence of reactive capillary hemangioma is high, mainly because SHR-1210 is an effective agonist of human vascular endothelial growth factor 2 that can activate vascular endothelial cells, and promote the occurrence of hemangioma.[34] These discoveries make the application of SHR-1210 and vascular endothelial growth factor inhibitor as a new combined anti-tumor strategy. The initial outcomes showed SHR-1210 had a manageable toxicity and promising antitumor activity; in addition, multiple studies involving SHR-1210 are ongoing (Table 1).

Durvalumab is a monoclonal immunoglobulin IgG1κantibody against PD-L1. In a phase I trial of durvalumab monotherapy for advanced solid tumors, 7 of 22 patients experienced grade 2 treatment-related AEs, and 1 patient experienced grade 3 treatment-related AEs; Nineteen patients were evaluated for efficacy, with 1 patient PR and 6 patients SD.[35] Currently, This study and other phase I/II clinical studies of durvalumab for esophageal cancer are still ongoing (Table 1).

SHR-1316, a humanized immunoglobulin IgG4 PD-L1 monoclonal antibody designed and produced in China, and has entered into various clinical studies in solid tumors. A multicenter, multi-country phase II clinical study of irinotecan/5-fluorouracil chemotherapy in combination with SHR-1316 in the treatment of advanced ESCC is well underway (Table 1), and the results including the primary endpoint of PFS are expecting.

CTLA-4 immune pathway inhibitor

In the Early stage of immune response, CTLA-4 plays a major role in regulating T cell proliferation, which is mainly located in lymph nodes. The CTLA-4 inhibitor combines with the CTLA-4 receptor and prevents the CTLA-4 receptor from binding to the B7 ligand on the antigen presenting cell surface, promoting T cell activation and proliferation to exert an anti-tumor effect. When T cells in peripheral tissues were activated, PD-1 was up-regulated and exerting immunosuppressive effect.[36] Therefore, the immunosuppressive response mainly occurred in peripheral tissues for PD-1/PD-L1 antibody; CTLA-4 pathway inhibitors cause more severe autoimmune diseases than PD-1/PD-L1 pathway inhibitors, which limits the clinical application of CTLA-4 inhibitors. Commonly used CTLA-4 inhibitors including ipilimumab and tremelimumab are mainly applied to clinical trials of malignant melanoma, non-small cell lung cancer and other solid tumors. To date, ipilimumab is approved for the treatment of advanced malignant melanoma because it can significantly improve the OS of patients with metastatic malignant melanoma.[37] However, ipilimumab did not distinctly improve OS in patients with NSCLC, and the incidence of grade 3–4 immune-related AEs was as high as 47%.[38] Moreover, a phase II trial (NCT01585987) about ipilimumab monotherapy for advanced gastric cancer and gastroesophageal junction cancer failed and was terminated.[39] Currently, the efficacy of CTLA-4 inhibitors in esophageal cancer remains unclear; And there are few studies on CTLA-4 inhibitors monotherapy for esophageal cancer, mostly CTLA-4 inhibitors combined with PD-1/PD-L1 inhibitors (Table 1).

Biomarkers predicting the efficacy of immunotherapy for ESCC

PD-L1

The significance of PD-L1 expression level in tumor cells is still controversial. Most scholars believe that PD-L1 expression in tumor cells is the most reasonable biomarker to predict

the therapeutic efficacy of PD-1/PD-L1 inhibitors.[12,19,40,41] Fehrenbacher et al indicated that the expression of PD-L1 was correlated with the therapeutic effect of PD-1/PD-L1 inhibitors.[42] In the KEYNOTE-180 trial, patients with PD-L1 CPS ≥10 had a higher 6-month-PFS rate (22% vs 10%) and 9-month-PFS rate (14% vs 5%) than those with PD-L1 CPS <10.[29] And the results of phase III KEYNOTE-181 trial revealed significant survival benefit in patient with PD-L1 CPS ≥10 with pembrolizumab. However, in a clinical trial of JS001, the preliminary results revealed that there was no relationship between clinical efficacy and PD-L1 expression.[31] Besides, Huang et al showed that the expression of PD-L1 was not significantly associated with ORR and DCR in the clinical trial of SHR-1210 for esophageal cancer.[33] Some patients with negative PD-L1 expression are effective in immune checkpoint inhibitors treatment, while some patients with positive PD-L1 expression are ineffective, in which these inconsistent results are mainly because of the heterogeneity of PD-L1 tumor expression, different samples submitted for examination and inconsistent detection standards, etc. In conclusion, it remains uncertain whether the tumor PD-L1 expression level is correlated with the efficacy of immunotherapy, and more evidence is needed to confirm the relationship between them in the future.

Tumor mutation burden (TMB)

TMB refers to the total amount of non-synonymous mutations in the tumor gene coding region; the higher TMB means the more neoantigens generated by tumor mutations, the more tumor-infiltrating T lymphocytes, and the stronger anti-tumor immune response.[43] Between different cancer classes, TMB was highly variable and ranged from 0.001 per megabase(Mb) to more than 400 per Mb.[44] And median numbers of TMB in esophageal cancer was lower than that in lung cancer and melanoma.[44] Several studies have shown that both PFS and OS are prolonged with the increase of TMB with immunotherapy, and TMB has the potential to be a biomarker to evaluate the efficacy of immunotherapy.[41,45–47] Rizvi and colleagues indicated that TMB had a strong correlation with clinical response in non-small lung cancer treated with PD-1 inhibitors.[48] Likewise, long-term benefit was also associated with a higher TMB in melanoma patients treated with CTLA-1 inhibitors.[49] Besides, Greally et al analyzed the relationship between TMB and survival in 62 patients of immunotherapeutic esophageal cancer, including 8 patients of ESCC; this clinical study found that the optimal critical value was 7.3 per Mb and indicated that patients in the high TMB group obtained significant survival benefits.[50] The numbers of ESCC patients were few in this study, and prospective randomized clinical studies are needed to identify and validate the optimal cut-offs value of TMB in ESCC that effectively predict response to immune checkpoint inhibitors in the future.

Microsatellite instability–high status (MSI-H)

Microsatellite instability-high status (MSI-H), also known as deficiencies mismatch repair (dMMR), is caused by mutations in the mismatch repair proteins MLH1, MSH2, PMS2, and MSH6, and induces more neoantigen emergence to increase immune cell infiltration.[51] Previous study on immunotherapy for colorectal cancer found there was a positive association between MSI-H and high TMB.[52] Le et al showed that the status of mismatch repair could predict clinical benefit of pembrolizumab and discovered that dMMR tumors were associated with prolonged PFS compared with mismatch repair-proficient tumors, regardless of the origin tissue of cancer.[53,54] So far, the NCCN guidelines have recommended pembrolizumab as second-line or subsequent therapy for MSI-H or dMMR esophageal cancer.[6] Although the incidence of MSI-H in ESCC is rare and only about 8%, this biomarker is very important and may affect the efficacy of immune checkpoint inhibitors.[55]

The analysis and verification of biomarkers that predict the efficacy of immune checkpoint inhibitors will optimize the selection of eligible patients with esophageal cancer for immunotherapy, and promote the individualization and precision of immunotherapy. To date, the prediction effect of single biomarker is limited, more attention should be paid to the combined prediction models of multiple biomarkers in evaluating the efficacy of immune in the future.

The combination therapy

In recent years immunotherapy combined with other anti-tumor strategies have attracted more attention, especially in malignant melanoma and non-small cell lung cancer. However, there is still a long way of immunotherapy in ESCC.

The most common combination of immune checkpoint inhibitors is PD-1/PD-L1 pathway inhibitors united with CTLA-4 pathway inhibitors. A global phase II clinical study of nivolumab alone or combined with ipilimumab for patients with advanced ESCC is ongoing.[56] In addition, multiple clinical studies of PD-1/PD-L1 inhibitors combined with CTLA-4 inhibitors for the treatment of esophageal cancer are also underway (Table 1).

Radiotherapy plays a significant role in the comprehensive treatment of ESCC. Radiotherapy can induce immune-mediated abscopal effects by re-recruiting T cells to enter the microenvironment, promoting the secretion of cytokines and enhancing the expression of tumor antigens.[57,58] Herrera et al proved that radiotherapy can directly induce the DNA damage in tumor cells, stimulate more tumor immuno-associated antigens releasing, and increase the infiltration of tumor T lymphocytes; however, radiotherapy can also up-regulate the PD-L1 expression of tumor cells and inhibit the anti-tumor activity of effector T cells, leading to radiotherapy resistance.[59] Radiotherapy combined with immunotherapy can not only improve the sensitivity of radiotherapy, but also harness the immune system to improve cancer therapy. Currently, multiple phase I/II clinical study of radiotherapy combined with immune checkpoint inhibitors for esophageal cancer is underway (Table 1).

Chemotherapy is an aggressive therapy to destroy rapidly growing cells in the body. Recent studies have shown that chemotherapy may have stimulated the immune system, which has the potential to induce favorable immunogenic conditions in tumor microenvironment.[60,61] Chemotherapy combined with immunotherapy can reverse the immunosuppression to some extent, improve the cross-presentation of tumor antigens, promote the proliferation of effector T cells, and enhances the anti-tumor function of the immune system.[62–64] Several clinical studies to explore the best combination of the two therapies are currently underway (Table 1).

Evaluation system of immunotherapy

Traditionally, the Response Evaluation Criteria in Solid Tumor (RECIST) has been used to evaluate the efficacy of antitumor treatment, but it is inappropriate to utilize this system in immunotherapy.[65–67] The anti-tumor response of immunotherapy is unobvious and persistent; although the tumor will continue to grow in the early stage of treatment, the patient can gain long-term survival benefits.[65] Immunotherapy cause an innate antitumor immune response, this is usually accompanied with the increase of tumor load at the early stage of treatment, the appearance of new antigen and the subsequent continuous disease stabilisation; therefore, the pseudoprogression of tumor are always discovered at the early stage of immunotherapy, and the RECIST may underestimate the efficacy of immunotherapy, leading to early termination of treatment.[65] For this reason, the immune-related response criteria such as irRC, irRECIST, iRECIST and imRECIST emerged.[67–70] In those evaluation criteria, the presence of new lesions does not necessarily indicate disease progression in the case of reduction of primary lesions, but may activate the immune response within the tumor.[67–70] Whereas, the immune-related response criteria are rarely used in clinical studies, and its accuracy and feasibility need to be further verified.

Hyper progression

Immune checkpoint inhibitors have shown promising anti-tumor activity, however, several studies showed accelerated disease progression in some patients treated with PD-1/PD-L1 inhibitors, which was known as hyper-progressive disease.[71,72] This new phenomenon is mainly correlated with the dilation of Tregs, depletion of compensatory T cells, restructuring of pro-tumorigenic immune cell subsets, activation of aberrant inflammation or activation of oncogenic signaling.[73,74] Hyper-progressive disease has been observed in NSCLS, melanoma and other malignancies; nevertheless, in the immunotherapy of ESCC, hyper-progressive disease has not been found so far.

Liquid biopsy

Liquid biopsy can obtain an extensive amount of information about the tumor through a simple blood sample, which is simple and non-invasive compared with surgical biopsies. Nicolazzo et al showed that PD-L1 expression in circulating tumor cells was correlated with poor clinical efficacy in patients with non-small cell lung cancer treated with nivolumab.[75] In addition, Koeppel et al also demonstrated that liquid biopsy could be applied to determine TMB using circulating cell-free DNA, particularly in cases where tumor biopsy was not accessible or had been resampled.[76] Dynamic evaluation of immunotherapy by liquid biopsy has shown certain advantages in other tumors, and it is expected to be applied and confirmed in ESCC.[77,78]

Multidisciplinary comprehensive treatment is important in the Anti-tumor therapy. At the time of initial diagnosis, most patients with ESCC are in advanced or metastatic stage and their disease progressed rapidly. Present existence treatment regimens have limited benefits for patients. For patients with advanced/metastatic ESCC who have failed in standard treatment, immunotherapy shows persistent anti-tumor activity and manageable safety profile, which creates a promising prospect for the application of immunotherapy in ESCC. At present, there are seldom biomarkers to accurately predict the effect of

immunotherapy; to some extent, PD-L1, TMB, MSI-H and other biomarkers are related to the efficacy of immunotherapy, and more prospective trials are needed for further study. The evaluation of immunotherapy efficacy by multiple biomarkers may become a direction for future research. The RECIST system is limited in the evaluation of the immunotherapy efficacy, and the optimal evaluation criteria for immunotherapy are being explored. In order to evaluate the most appropriate time window for the combination of immunotherapy and traditional anti-tumor strategies to maximize the anti-tumor benefit of combination therapy and minimize the adverse reactions, a number of studies in ESCC patients are currently under investigation (Table 1). Anyway, immunotherapy is an exciting treatment in the emerged antitumor strategies.

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