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ARTICLE

Research Progress of the Treatment of PD-1 Immune CheckpointInhibitors in Oral Squamous Cell Carcinoma

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ABSTRACT

Targeted immune checkpoint-based immunotherapy has achieved remarkable success in the treatment of malignant tumors. Immune checkpoint inhibitor-programmed cell death protein 1 (PD-1) antibody opens a new era of immunotherapy for platinum-refractory recurrent/metastatic oral squamous cell carcinoma (OSCC). The overall survival of patients treated with immunological checkpoint inhibitors was significantly prolonged, and the overall incidence of grade 3-4 drug-related adverse events (AEs) occurred was lower; however, there are still some challenges to the PD-1's application in OSCC clinic treatment. This article is just to briefly highlight the development of such application to date.

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common malignant tumor category worldwide. Oral carcinoma, the most common subcategory of HNSCC, can be the 9th - if alone - on the same ranking list. Each year, more than 300,000 people are affected by oral carcinoma, in which OSCC accounts for 90%. At present, the treatment of OSCC mainly consists of traditional surgery, radiotherapy and chemotherapy. More than 50% of OSCC patients have tumor recurrence or metastasis within 3 years; and more than 145,000 patients die from oral malignant tumors each

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year. The recorded 5-year survival rate is about 50% [1-4].

In recent years, with the development of research on the relationship between immunity and tumor, immunotherapy has become an important means of tumor therapy further to traditional surgery, radiotherapy and chemotherapy. In 2018, Prof. Allison and Prof. Honio won the Nobel Prize in Physiology or Medicine for their research work on cytotoxic T lymphoid-associated antigen-4 (CTLA-4) and PD-1 in the immune checkpoint. Since 2010, the immunosuppressive checkpoint molecules have been recognized as new targets for immunotherapy, whose curative effectiveness was initially demonstrated in treatment of advanced melanoma and then gradually applied to different types of malignancies with varying degrees of benefit. In the second half of 2016, two PD-1 immune checkpoint inhibitors, Nivolumab (Opdivo) and Pembrolizumab (Keytruda), were approved by the FDA for treating relapsed and refractory HNSCC. This means currently there are two PD-1 immune checkpoint inhibitors approved for treating OSCC. According to the current research progress, compared with the traditional treatment, PD-1 immunocheckpoint inhibitor has better prospect on treatment of advanced OSCC.

2. Immune Checkpoint Protein

As the core executor in the process of anti-tumor immunity, T cells have two types of stimulation signal molecules on their surface, namely, co-stimulation molecules and co-inhibition molecules. The process which T cells exert an immune response involves being activated first by antigen recognition signal, and then fine-regulating T cell response by co-stimulating signal molecules. The co-inhibition molecules that play a negative immune regulatory role are also called immune checkpoint molecules. Common checkpoint proteins in tumor immunotherapy include PD-1, CTLA-4, T cell immunoglobulin and Mucin Domain 3(TIM-3), LAG 3, T cell immunoglobulin and ITIM domain (TIGIT), etc. Among which the PD-1 and CTLA-4 are most focused due to apparent effectiveness of their functions in treatment of malignant tumors.

3. Biological Characteristics of PD-1 and Its Ligand

A member of the CD28 superfamily, PD-1, was originally cloned from apoptotic small T cell hybridoma 2B4.11 and is the immunoglobulin superfamily Type I transmembrane glycoprotein. It is mainly expressed on the surface of activated T lymphocytes, NK cells, monocytes and B lymphocytes. As an important immune checkpoint for immunosuppression of tumor-infiltrating T cells, PD-1 is up-regulated in a variety of tumor microenvironments, such as gastric cancer, ovarian cancer, pancreatic cancer, hematologic tumors, etc. PD-1 exists as monomer on the cell surface and is composed of an extracellular IgV region, a transmembrane domain, and an intracellular tail [5]. There are four N-ligand glycosylation sites in the extracellular immunoglobulin - like domain for binding to ligands. There are two tyrosine residues in the intracellular area: the terminal N is the immunoreceptor tyrosine-based inhibitory motif (ITIM), and the terminal C is immunoreceptor tyrosine switch motif (ITSM).

PD-1 receptor has two ligands: PD-L1 (CD274/ B7-H1) and PD-L2 (CD273/B7-DC). PD-L1 has a wider expression spectrum than PD-L2, and is mainly expressed in hematopoietic and non-hematopoietic cells (including epithelial cells, vascular epithelial cells, stromal cells, etc.). Under the action of inflammatory factors (including type I and type II interferon, TNF-α and VEGF) or tumor cells, PD-L1 is induced to be expressed in stromal cells and tumor cell surfaces of tumor tissues. PD-L1 is highly expressed in many solid tumors, such as non-small cell lung cancer, melanoma, prostate cancer, breast cancer, renal cell carcinoma, etc [6-7], also in HNSCC.

Current studies have shown that PD-1 binding with ligands blocks the activation of T cells and thus blocks their proliferation through the following pathways, to make the T cell immune response incompetent: First, in the case of simultaneous mating with T cell receptor (TCR), the phosphatase SHP-2 with the SH2 domain is recruited by the intracellular ITSM to block the phosphorylation mediated by the activation of TCR molecules. This prevents T cell activation and cytokine production. Secondly, the combination of PD-1 and PD-L1 can inhibit the activation of CD28-mediated phosphoinositide-3-kinase (PI3K), dephosphorylate the phosphatidylinositol 3-kinase B -protein kinase B (PI3K-AKT), and thus inhibit T cell activation. This inhibitory effect of PD-1 can be reversed by enhanced CD28 or signal transduction and activator of transcription (STAT) cytokines.

Based on the mechanism described above, PD-1 inhibitors, and PD-1 ligand PD-L1 inhibitors, block the interaction between PD-1 and PD-L1, thereby blocking the immune escape of tumors. Blocking the PD-1/PD-L1 signaling pathway has achieved a relatively long-lasting anti-cancer response. With breakthrough progress of efficacy on the treatment of various malignant tumors such as melanoma, non-small cell lung cancer, Hodgkin's lymphoma, genitourinary system tumors, colorectal cancer, etc., PD-1 inhibitors continues to expand its tumor

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treatment spectrum [8].

PD-L2 and PD-L1 share 37.4% homology at the gene level. PD-L2 mainly involves in regulating the immune response caused by natural environmental antigens. The expression and regulation mechanisms of PD-L1 and PD-L2 are different. Previous studies have shown that PD-L2 is mainly expressed in dendritic cells, monocytes, mast cells derived from bone marrow, and B cells in the germinal center. Also, it's slightly expressed in vascular endothelium and T cells. Recent studies have used innovative immunohistochemical methods to analyze more than 400 tissue samples involving 7 different types of tumors, including renal cell carcinoma, bladder cancer, melanoma, non-small cell lung cancer, triple negative breast cancer, gastric cancer, and HNSCC. The results showed that there was no PD-L2 expression in the tumor cells of renal cell carcinoma tissue samples; very few tumor cells expressed PD-L2 in melanoma samples; the expression level of PD-L2 was significantly increased in gastric cancer and triple-negative breast cancer; and more than half of tumor cells overexpress PD-L2 in HSNCC tissue samples [9].

4. PD-1 and Its Ligand: Their Expression in OSCC and Anti-Tumor Efficacy

As the main ligand of PD-1, PD-L1 is not only overexpressed on the surface of t, umor cells in OSCC, but also expressed on the surface of immune cells in the tumor microenvironment, including regulatory T cells (Tregs), natural killer (NK) cells and Antigen presenting cells (APCs) [10-12]. Previous studies showed that the expression of PD-1 and PD-L1 on the surface of CD4+ and CD8+ T cells in the peripheral blood of OSCC patients was significantly higher than that of the control group; also, the study found that the level of soluble PD-1 in the plasma of OSCC patients was also significantly higher than the control group [13]. In addition, the expression of PD-1 in the peripheral blood of patients with OSCC or with precancerous lesions of actinic cheilitis (AC), is higher than that of normal people, while the expression of PD-1 on CD4+ and CD8+ T cells in the tumor site of OSCC patients was higher than that of the AC ones [14]. Another study showed that compared with normal oral mucosa, the expression of PD-L1 in OSCC is significantly up-regulated, and such expression of PD-L1 in peripheral blood of patients with lymph node metastasis is significantly higher than that of patients without lymph node metastasis. Research suggests that in addition to the local area of the tumor, the expression of immune checkpoints in the entire system should also be considered [15].

The correlation between the expression or threshold of PD-1 ligand and the anti-tumor immune efficacy of PD-1 immune checkpoint inhibitors remains unclear. Reviewing the approved clinical trials of PD-1/PD-L1 drugs, the current expression of PD-L1 is basically an item for mandatory check. Known results suggest that to most cancers approved to be treated with immune checkpoint inhibitors, such as non-small cell lung cancer, melanoma, urothelial carcinoma, OSCC (HNSCC), etc., PD-L1 expression is positively correlated with the objective response rate and/or survival time [16]. It is currently believed that the expression of PD-L1 in tumor cells exceeding 10% is related to a poor prognosis, and it is generally regarded as a demarcation point related to clinical efficacy. Related studies showed that the PD-L1 expression rate of OSCC samples is 10% to 15%, which is negatively correlated with tobacco and alcohol consumption, and PD-L1 expression is correlated with tumor recurrence and survival rate [17]. However, there are still some defects of PD-L1 expression in clinical applications: (1) The expression of PD-L1 in some tumors (such as renal cell carcinoma) has no correlation with clinical benefit; (2) Even in the same type of tumor, the relationship between the expression of PD-L1 and the efficacy may be contrary to the prediction [18].

There are few studies on the correlation between PD-L2 and PD-1 immune checkpoint inhibitors in anti-tumor efficacy. Current researches suggest that PD-L2 is overexpressed on the surface of OSCC tumor cells. Jennifer Yearley's study showed that among 172 patients with relapsed or metastatic HNSCC treated with pembrolizumab, the ORR of patients with PD-L1 and PD-L2 expression both positive was 27.5%, while the ORR of patients with positive PD-L1 expression and negative PD-L2 expression was only 11.4%.Therefore, the expression level of PD-L2 can be used as supplementary information, together with the expression level of PD-L1, as predictors of tumor efficacy [5]. This emphasizes the importance of PD-L2 expression, which is conducive to a better understanding of the tumor biological significance of PD-1 signaling pathway.

5. Application of PD-1/PD-L1 Checkpoint Inhibitors in OSCC Treatment

Since the second half of 2016, nivolumab and pembrolizumab have been approved by FDA for the treatment of oral cancer. Pembrolizumab, also known as MK-3475, is the first PD-1 monoclonal antibody approved for clinical trials of recurrent/metastatic HNSCC. Among the 132 patients in the experimental group of the multicenter phase I

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clinical trial (KEYNOTE-012), 49.3% of them obtained partial response or stable disease, of which 78% were PD-L1 positive patients, the response rate of PD-L1 positive patients was 20%, and 86% of patients showed a durable response. The patients who received a response after treatment in this study included HPV+ patients as well as HPV- patients. Research showed a low incidence of adverse drug reactions, with only 7.6% of patients with> grade 3 drug-related adverse reactions [19].

Pembrolizumab has shown anti-tumor activity and controllable drug toxicity in early trials. The phase III clinical study KEYNOTE-040 further observes its efficacy and safety. From December 24, 2014 to May 13, 2016, 247 patients were randomly assigned to the pembrolizumab group, and other 248 patients were randomly assigned to the standard chemotherapy group. As of May 15, 2017, 181 (73%) patients in the pembrolizumab group and 207 (83%) patients in the standard treatment group had died. The median overall survival of the pembrolizumab group and standard treatment group was 8.4 months vs. 6.9 months respectively; and the overall incidence of> grade 3 drug-related adverse reactions in the pembrolizumab group was lower (33 cases [13%] vs 85 cases [36%]). The most common treatment-related adverse events of pembrolizumab were hypothyroidism (33 cases [13%] patients) and fatigue (43 cases [18%]) [20]. Another phase III clinical study (KEYNOTE-048) was made based on platinum-resistant HNSCC patients with relapse and metastasis, its intermediate study results were announced in 2018 by the European Society of Medical Oncology (ESMO): Compared with the standard chemotherapy regimen EXTREME (PFE: carboplatin/cisplatin, 5-FU, cetuximab + cetuximab maintenance), among the 882 patients who used pembrolizumab as the first-line treatment, the combined positive score of PD-L1 expression (CPS. The number of PD-L1 positive cells in tumor cells, lymphocytes, and macrophages) was ≥20 with an OS rate of 39%, while OS was only 22% in the group of patients CPS ≥1.

In the multicenter phase III clinical study (CHECKMATE-141) of Nivolumab for the treatment of platinum-resistant recurrent or metastatic HNSCC, the overall survival of patients receiving nivolumab (240 cases) and docetaxel treatment were 7.5 vs 5.1 months respectively. The 1-year overall survival rate was 36.0% vs 16.6%, and the study showed that in nivolumab treatment, the overall incidence of drug-related adverse reactions of >3 grade was lower (13.3% vs 35.1%) [22]. Based on the above research data, in November 2016, the FDA approved nivolumab for the treatment of patients with recurrent or metastatic HNSCC [22].To observe the long-term efficacy and safety of the drug on PD-L1-expressing patients, a preliminary analysis with 2-year follow-up was made and it showed that Nivolumab can significantly improve OS and maintain controllable and consistent safety. But at the same time studies also showed that OS has no correlation with PD-L1 expression and HPV infection status. However, in the treatment of Pembrolizumab, the results of KEYNOTE-040 and KEYNOTE-048 support that PD-L1+ can significantly improve the survival time of patients.

In the phase I clinical trial of HNSCC, PD-L1 antibody also showed a certain degree of clinical efficacy. Currently, representative antibodies targeting PD-L1 include durvalumab (MEDI-4736), atezolizumab (MPDL3280A) and BMS-936559 (MDX1105), which have been used as monotherapy or in combination with other drugs in clinical trials of multiple tumors [23]. The durvalumab (IgG1 isotype) study recruited 62 patients with R/M HNSCC. The results of the study showed an ORR of 12%, and a sustained response time of 4 to 43 weeks was obtained. The response rate of PD-L1 positive patients was 25%. The 24-week disease control rate of all patients was 16%, which was 25% of PD-L1 positive patients [24]. In addition, there are randomized phase I/II clinical trials evaluating durvalumab combined with AZD9150 or AZD5069 (NCT02499328) for patients with metastatic HNSCC. The study is currently evaluating clinical safety, efficacy and ORR [26]. There are few studies on Atezolizumab in the treatment of HNSCC. According to the clinical deadline of April 30, 2013, a study included a total of 277 patients with advanced cancer, with a response rate (RR) about 17%, but the number of HNSCC was small (n = 6) [26]. Currently in clinical trials of HNSCC, PD-L1 antibody is combined with other immune checkpoint inhibitors to improve efficacy. Some trials evaluating the combination of durvalumab monotherapy and tremelimumab (anti-CTLA-4) are ongoing (NCT02551159, NCT02369874, NCT02319044), and the clinical results of such immunotherapy combinations are highly anticipated [27,28].

6. Problems and Challenges of PD-1 Immune Checkpoint Inhibitors in OSCC Treatment

PD-1 immune checkpoint inhibitors currently have achieved good clinical effects in the treatment of HNSCC and other malignant tumors, but only a small number of patients can benefit from monotherapy. Therefore, in order to improve the disease response rate and long-term efficacy, some preclinical studies and clinical trials have used PD-1 combined with radiotherapy, radiotherapy, targeted drugs and other immune checkpoint inhibitors for

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the treatment of HNSCC, and achieved varying degrees of clinical efficacy initially. Such as Pembrolizumab combined with cetuximab in the treatment of HNSCC (NCT02586207) [29]. Pembrolizumab combined with platinum drugs or radiotherapy is used for neoadjuvant treatment of HNSCC surgery, exploring the use of pembrolizumab for resectable HPV-negative, and neoadjuvant and/or postoperative adjuvant treatment of patients with stage III/IV HNSCC [30-31].

Although a number of trials have confirmed the effectiveness and the short-term safety of anti-PD-1/PD-L1 pathway in the treatment of tumors, preliminary clinical research data showed that patients with different types of malignant tumors, including OSCC patients, have primary resistance to PD-1/PD-L1 drugs as high as 60%, therefore, it is urgent to further improve the treatment response rate and long-term efficacy [32]. Since the PD-1/PD-L pathway plays an important role in autoimmune regulation and tumor immunity, with the complexity of the tumor microenvironment, the primary drug resistance mechanism of PD-1 antibodies is also complicated. The current research on the resistance mechanism of PD-1 antibodies mainly proposes the following points: weak tumor cell immunogenicity, limited immune cell infiltration within the tumor, tumor burden factors, different mismatch repair(dMMR) in solid tumors, and multiple expressions in the tumor microenvironment(TME) inhibitory receptors and pathways of immunosuppression induced by TME, etc. [33-35].

In response to the problem of resistance to PD-1 immune checkpoint inhibitors in the treatment of OSCC, besides improving the efficacy through combination with other treatments, researchers are also actively exploring resistance mechanisms and other solutions. Finding biomarkers for predicting efficacy is an effective way to achieve precision treatment of OSCC. Most current studies believe that PD-1/PD-L1 inhibitors have higher benefits for patients with PD-L1 positive tumors. Based on the current research results, it is still uncertain whether the effective rate of PD-1 inhibitors in the treatment of OSCC will be affected by the expression level of tumor PD-L1. Based on the current studies, there is currently no evidence that HPV infection is directly related to the effective rate of PD-1 inhibitors and the durable response rate of patient [36]. The expression level of PD-L2 can be used as supplementary information, combined with the expression of PD-L1 to be a predictor of efficacy.

In addition, the composition of the digestive tract microbial population is related to immune disorders and the occurrence and development of many malignant tumors. Two retrospective clinical studies emphasized that the application of antibiotics will affect the efficacy of immunotherapy, and proposed that to the patients with advanced tumors suppress immune checkpoints, their drug resistance (especially the PD-1/PD-L1 antibody) can be caused by the abnormal composition of intestinal microbes [37-38]. OSCC originates from the oral mucosal epithelium, and the oral microbiota is often exposed to external environmental factors. Compared with healthy controls, OSCC patients have a different microbiota composition in saliva, and the presence of specific bacteria is associated with the risk of OSCC. Current studies also found that the composition of the microbial population is related to the expression of HPV. The correlation between the composition of oral microbes and the resistance of immune checkpoint inhibitors needs to be further confirmed [39].

Immune checkpoint inhibitors have opened a new era of tumor immunotherapy, and PD-1 inhibitors have an important role in promoting the efficacy of OSCC treatment. However, the drug currently also faces a series of problems in clinical application, including clinical efficacy and immunotherapy-related side effects. To solve these problems, the researchers still have a long way to go.

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