Advances of immune checkpoint blockade in the treatment of advanced gastric cancer

Zhi-Jia Sun, Nan Du

Department of Oncology, Chinese PLA General Hospital, Beijing 100853, China

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ABSTRACT

The treatment of advanced gastric cancer has been a worldwide problem, and the curative effects of chemotherapy and targeted therapy are limited for advanced gastric cancer. With the widespread use of immune checkpoint blockade in clinical studies, immunotherapy provides new opportunities for patients with advanced gastric cancer. Cytotoxic T lymphocyte associated protein 4 (CTLA-4), programmed death protein 1 (PD-1) and its ligand (PD-L1) are the most thoroughly studied in the immune checkpoints, and the latest research data show good treatment prospects. Whether it is used as single therapy or combined with other treatment, immunological checkpoint inhibitors have achieved good results. How to choose the appropriate immunotherapy as well as the appropriate dose, combination, interval and length of treatment is the problem we will have to pay attention to in the next step.

1. Introduction

The treatment of advanced gastric cancer has been a worldwide problem, chemotherapy can only improve the median survival and overall survival of advanced gastric cancer to a certain extent, and its treatment effect is very limited. Although targeted therapy brings new hope to some patients, there are still some limitations. Trastuzumab is mainly used in the HER-2-expressed gastric cancer, while Ramucirumab is only limited to second-line treatment[1]. With the proposing of new classification of gastric cancer, immunotherapy is considered to be a major breakthrough in the treatment of gastric carcinoma in recent years, and the immune checkpoint blockade[2] that uses programmed death-1 (PD-1) and programmed death ligand 1 (PD-L1) antibody has become a focus in the study of immunotherapy.

The Cancer Genome Atlas (TCGA) suggests dividing the gastric cancer into four subgroups, among which the microsatellite instability (MSI) subgroup and EB virus infection (EBV) subgroup account for 22% and 9% respectively. The former is characterized by MLH1 promoter supermethylation, including the elevated incidence of gene mutation that encodes cancer-causing signaling transduction protein, etc.; the latter is characterized by DNA hypermethylation, especially the CDKN2A promoter hypermethylation, the PIK3CA gene mutation and PD-L1/2 over-expression[3]. The tumor immune response plays an important role in the two subgroups, and the immunotherapy that blocking tumor antigenic escape is the effective method for the treatment of patients with these subgroups of gastric cancer.

2. Immune checkpoints

The immune system can specifically identify and eliminate tumor cells based on the tumor specific antigens or the expression of molecules induced by cell stress. T lymphocytes have an immune surveillance function that prevents the tumor from developing[4].
There are several immune checkpoints on T cell membrane surface, these "checkpoints" can inhibit T cell function under normal circumstances, and meanwhile, cancer cells can be targeted to select these inhibitory mechanisms and prevent continuous T cell response to auto-tissue. Thus, selective blocking of these natural inhibitory checkpoints can continue to activate the T cells, thereby activating and promoting effective anti-tumor response. In immune inhibitory checkpoints, cytotoxic T lymphocyte associated protein 4 (CTLA-4), programmed death protein 1 (PD-1) and its ligand (PD-L1) are the most thoroughly studied, and the clinical studies on their inhibitors at home and abroad have achieved good results.

2.1 CTLA-4

CTLA-4 is mainly expressed in CD4+T cells, and the ligands (B7-1 and B7-2) are expressed only in the antigen presenting cells instead of on the surface of the tumor cells. CTLA-4 competes with CD28 to be combined with B7-1 and B7-2, then induce T-cell nonreactivity, and participate in negative regulation of immune response. So blocking the CTLA-4 can cause T cell activation[5]. Many preclinical mouse models have studied the blocking effects. In the study of mouse models established by Peggs and others, the CTLA-4 blockade increases the rejection reaction of the transplanted tumor and promotes the rejection reaction of the tumors that have been developed[6].

2.2 PD-L1/PD-L2

PD-1 is the negative regulatory co-stimulatory receptor that is mainly expressed on activated T cells, which is combined with its ligand PD-L1 (or B7-H1) and PD-L2 to inhibit T cell migration, proliferation and effector function. PD-L1 is expressed in immune cells and some non-hematopoietic cells; PD-L2 is mainly expressed in antigen presenting cells[7]. In addition, the high expression of PD-L1 and PD-L2 is also detectable in tumor cells[8]. Since the PD-L1 is massively expressed in natural killer cells, dendritic cells, macrophages and mast cells, and can also be induced by inflammatory cytokines in various types of tumor cells, the PD-1 blockade can not only influence the early immune response in lymphoid tissue, but can also affect the late response in other parts[9].

2.3 Immune checkpoint role in prognosis of gastric cancer

The study of Wu C team[10] has shown that PD-L1 cannot be detected in normal stomach tissue, but is detectable in 42.2 percent of gastric cancer tissue. PD-L1 expression is not correlated with age, gender, tumor location or tumor differentiation in stomach cancer. However, PD-L1 expression is significantly correlated with tumor size, invasiveness, lymph node metastasis and patients’ survival time. When the tumor infiltrates to the deep muscular layer, the PD-L1 immunolabeling is significantly enhanced ($P<0.01$), and lymph node metastasis or survival is less than two years. HOU J and others[11] have observed the expression of B7-H1 in gastric cancer tissues, and found that the expression of B7-H1 is significantly higher in patients with lymph node metastasis and advanced clinical pathologic stage ($P<0.05$), the overall survival rate is lower in patients with enhanced expression of B7-H1 and the prognosis is worse ($P<0.05$). However, Kim and others[12] have found after evaluating the 243 cases of gastric cancer patients that have already had surgical resection that positive PD-L1 and CTLA-4 expression are observed in 43.6% and 65.8% of patients respectively. Among them, PD-L1 expression is associated with the better disease-free survival (DFS) and overall survival (OS) in gastric cancer. 5-year DFS of patients with positive and negative PD-L1 are 82.6% and 66.9% respectively, and the 5-year OS are 83.0% and 69.1% respectively.

PD-L1 positive and its prognostic value remain controversial, and the different results may be related to different patient populations, such as race, disease stage, different antibodies and so on. But most of the existing evidence supports the significance of PD-L2 over-expression in bad prognosis of advanced gastric cancer, and the condition after curative resection still needs further exploration and evaluation[13].

3. Immune checkpoint inhibitor research progress

3.1 CTLA-4 inhibitors

3.1.1 ipilimumab

Ipilimumab is the fully human monoclonal immunoglobulin that specifically blocks CTLA-4 specific, which blocks the CTLA-4 to strengthen the anti-tumor immune response and suppress tumor growth over the long term. It has been confirmed in two global III clinical research (MDX010-20 and CA184-024) about ipilimumab that both untreated and treated patients with advanced melanoma have obtained significant survival benefit. In NCT01585987 study[14], however, Ipilimumab and best support therapy (mostly chemotherapy) are used respectively as follow-up and maintenance treatment after first-line therapy in advanced gastric cancer and esophageal cancer, and the preliminary results show that the median overall survival is not significantly different between the two groups (12.1 months vs. 12.7 months).

3.1.2 tremelimumab

Tremelimumab is a kind of IgG2 monoclonal antibody inhibiting CTLA 4 receptor, and the study about tremelimumab III stage in
second-line treatment of advanced gastric cancer and esophageal cancer shows that the response rate (ORR) of 18 patients is only 5% and the median OS is 4.8 months\textsuperscript{[15]}. The study also confirms that the median survival of the patients with the posttreatment carcinoembryonic antigen proliferation response is higher than that of patients without response (17.1 months vs. 4.7 months, \textit{P}=0.004). Although the CTLA-4 inhibitor has achieved remarkable results in advanced melanoma and it has been approved by the U.S. food and drug administration (FDA), the results of ipilimumab and tremelimunab in gastric cancer remain unsatisfactory.

### 3.2 PD-1/PD-L1 inhibitors

#### 3.2.1 pembrolizumab

Pembrolizumab is a humanized high-affinity IgG4-κ monoclonal antibody that blocks the interaction between PD-1 and its ligand by combining PD-1. The further study and discussion of a multicenter and open-labeled 1b phase trial of pembrolizumab\textsuperscript{[16]} shows that in patients with mostly pretreated PD-L1-positive advanced gastric cancer, pembrolizumab is with controllable toxicity and antitumor activity, the treatment with pembrolizumab has caused sustained antitumor response in 22% of patients, median progression-free survival is 1.9 months (95% CI 1.8-3.5), and the median overall survival is 11.4 months. The overall toxicity curve of the population is similar to that of pembrolizumab, which is previously reported in patients with other advanced malignancies. There are no other toxic effects, and only five (13%) of the 39 patients have had a level 3 or 4 treatment-related adverse events. In addition, there is no permanent termination or death due to pembrolizumab treatment. The study shows that the use of pembrolizumab is a good treatment in contrast to many second-line chemotherapy. Interestingly, although the inclusion of the study requires PD-L1 positive, eight out of 35 patients with re-biopsy are negative. This factor may have influenced this outcome. The possible explanation is that the PD-L1 state is altered by prior chemotherapy or the PD-L1 state is heterogeneous in the entire tumor \textsuperscript{[17]}. For whatever reason, the study of PD-L1 state and its correlation with immune response in patients with stomach cancer remain to be explored.

#### 3.2.2 nivolumab

Nivolumab works by blocking the negative regulator of T-cell activation and response, thus allowing the immune system to attack the tumor. In the Checkmate 032 study\textsuperscript{[18]}, the preliminary results from the 59 patients that use nivolumab alone show that ORR is 12%, and the median response duration of the responders is 7.1 months. The response rates of PD-L1 positive and negative patients are 18% and 12% respectively. Of course, the result is also worth discussing because PD-L1 states are unstable in the pembrolizumab experiment. Only 14% of patients in the overall trial have a level 3 or 4 toxicity and there is no treatment-associated death.

### 3.2.3 avelumab

Avelumab is a fully humanized PD-L1 IgG1 monoclonal antibody, and it is found in the 1b phase study on gastric cancer and gastroesophageal combined with adenocarcinoma by Chung and others\textsuperscript{[19]} that the overall ORR of 20 patients who accept Avelumab as second-line chemotherapy is 15%, and PFS is 11.6 weeks. For 55 patients who receive avelumab as a maintenance treatment after first-line chemotherapy, the ORR is 7.3% and the PFS is 14.1 weeks.

In addition, the related trials of PD-1/PD-L1 inhibitors, such as durvalumab and atezolizumab also demonstrate the effectiveness in advanced gastric cancer, and further trials are ongoing.

### 3.3 Immunosuppressive therapy combination

#### 3.3.1 Double checkpoints inhibition

Since CTLA-4 and PD-1/PD-L1 inhibitors modulate different inhibitory pathways, the combination of antibodies targeting the two molecules may cause a stronger immune response. Clinical trials of nivolumab combined ipilimumab have shown the higher objective response rate and overall survival rate in patients with melanoma\textsuperscript{[20]}. In Checkmate012 trials, nivolumab combined with ipilimumab in non-small cell lung cancer (NSCLC) treatment has shown good safety and tolerability, and the results show higher reaction rate and lasting reactivity\textsuperscript{[21]}. In NCT01928394 study, different doses of nivolumab combined with ipilimumab are used in the treatment of advanced gastric cancer, and it is observed that compared with patients with PD-L1 negative, patients with PD-L1 positive are with better reaction of combination of the two; 27%-45% of combined treatment group of patients have a level 3 or higher toxic response. The experiment is still under way.

#### 3.3.2 Immunosuppressive therapy combined with targeted therapy

Preclinical evidence indicates that the combination of trastuzumab and PD-1 can enhance the effectiveness\textsuperscript{[22]}. At present, it is being studied about the efficacy and safety of Trastuzumab or cetuximab combined with pembrolizumab (NCT02318901) for patients with breast cancer, gastric cancer, head and neck cancer, and colorectal cancer. High levels of vascular endothelial growth factor (VEGF) can block the function of dendritic cells, and VEGF targeted therapy can reduce the level of VEGF to enhance antitumor immune response\textsuperscript{[23]}. The combination of VEGF and PD-1/PD-L1 for advanced gastric cancer treatment is worth further study. The use of effective targeted therapies and the release of tumor antigens will activate stronger specific immune response\textsuperscript{[24]}.
3.3.3 Immunosuppressive therapy combined with chemotherapy or radiotherapy

Both chemotherapy and radiotherapy can induce tumor antigen presenting and PD-L1 expression increase[25,26]. A ongoing nonrandomized experiment NCT02730546 is studying the efficacy and safety of Pembrolizumab combined with chemotherapy (paclitaxel plus carboplatin) and radiotherapy before surgical resection of resectable advanced gastroesophageal junction or gastric cardia cancer, and the result is worth looking forward to.

3.3.4 Immunosuppressor combined with other immunotherapeutics

Co-stimulatory receptor 4-1BB (CD137/TNFSF9) is expressed on T cells and antigen-presenting cells, and the main effect is to promote the activated anti-tumor cytotoxicity CD8T cell survival and amplification as well as its effector function[27]. In theory, the combination of checkpoint inhibitors and excitatory antibodies for the co-stimulatory receptors should achieve higher anti-tumor T-cell activity. NCT02179918 is a pharmacokinetic and pharmacodynamic study that aims to estimate the maximum tolerance of PF-05082566 (a 4-1BB agonist monoclonal antibody) and MK-3475 (a PD inhibitor) in patients with solid tumor. The effectiveness and safe dose of the combination of the two for advanced gastric cancer are worth further exploration.

4. Related toxicity of immune checkpoint blockade in treatment

It is important to note that these immune regulators have immunity-mediated toxicity[28]. These side effects are mainly caused by increasing the active state of other T-cell groups in the patients, and the adverse events include dermatitis, colitis, hepatitis, pancreatitis, pneumonia, and so on. However, these side effects can be controlled by using immunosuppressants such as corticosteroids, and will not interfere with the clinical effects of immune checkpoint blockade.

4.1 Dermal toxicity

Dermal toxicity is one of the most important adverse reactions, which is often dose-limiting and can lead to a cessation of treatment. Ipilimumab is mainly characterized by the skin itch and measles-like changes of the torso and limbs. The more severe dermal toxicities that have been reported include toxic epidermal necrolysis and severe drug rash complicated by eosinophilia and systemic symptoms[29]. The most common dermal adverse events of nivolumab and pembrolizumab include lichenoid reaction, eczema, vitiligo and itch[30].

4.2 Other toxicities

In addition to dermal toxicity, those specifically associated with patients with advanced gastric cancer include inflammatory colitis, hepatitis, gastrointestinal symptoms and weight loss, etc.[31]. The treatment-associated hepatic toxicities can be observed in many patients, such as the rise of the alanine aminotransferase (ALT) and aspartate aminotransferase (AST). When nivolumab and pembrolizumab are combined, the liver damage will be worse[32].

5. Conclusion and prospect

Immunotherapy has been a hot topic in the treatment of advanced gastric cancer, and immune-checkpoint blockade is one of the most promising treatments. We have seen the powerful effects of immune checkpoint inhibitors in melanoma and NSCLC, and the research results of advanced gastric cancer have surprised researchers. Although the results of the CTLA-4 inhibitor monotherapy in gastric cancer remain unsatisfactory, the study of PD-1/PD-L1 inhibitors and immunotherapy combinations is encouraging. Trastuzumab is the first targeted therapy drug approved for advanced gastric cancer patients with 20% HER2 overexpression[33], and immune checkpoint blockade treatment seems to be mainly aimed at advanced gastric cancer patients with 22% MSI and 9% EBV[34,35]. Therefore, more research is needed to determine how to optimally choose the right patients and the right treatment. Several of the currently studied hot genes include HER2, CCND1, EGFR and MYC, and PD-L1 and PD-L2 in particular, have been amplified in gastric cancer. These genetic abnormalities can predict which individuals will best respond to targeted therapies. In addition, we can see the initial results of the immunotherapy combination, further clinical trials are ongoing and the results are expected. Now we need to focus on how to choose appropriate immunotherapy, as well as the right dose, combination, time interval, course of treatment, and so on, which are still under exploration.

References


