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MINIREVIEWS

PD-1/PD-L1 antagonists in gastric cancer: Current studies and perspectives

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Abstract

Immune checkpoints release suppressive signals for T cells, which enable the tumors to escape from immune destruction and provide a new concept that uses the capabilities of the immune system as a therapeutic target for tumors. At present, programmed death receptor 1 (PD-1)/programmed death ligand-1 (PD-L1) has become the most promising therapeutic target. PD-1/PD-L1 blockades exhibit long-lasting antitumor efficacy and safety in patients with various cancers, such as melanoma and non-small-cell lung cancer. Moreover, PD-L1 is highly expressed in the peripheral blood and tumor specimens of patients with cancer, and the expression of PD-L1 is positively correlated with various pathological features and may serve as a predictor of poor prognosis or a diagnostic tool. Clinical trials have verified that PD-1/PD-L1 blockade therapy benefits patients with advanced gastric cancer or gastroesophageal junction cancer. Furthermore, there are many molecules involved in the regulation of PD-1/PD-L1 expression, and the modification of these molecules *via* drugs and combinations with PD-1/PD-L1 inhibitors may further improve the efficacy of immunotherapy for gastric cancer. In this review, the efficacy, safety, and possible combination treatment options of PD-1/PD-L1 in gastric cancer are reviewed in experimental and clinical settings.

Key words: Immunotherapy; PD-1/PD-L1 inhibitors; Programmed death-ligand 1; Gastric cancer

Core tip: Programmed death receptor 1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors have been defined as a distinct type of immunotherapy for various cancers. A growing number of studies have investigated the role of PD-1/PD-L1 inhibitors in gastric cancer. This manuscript presents a comprehensive overview of the mechanism of PD-1/PD-L1 blockade therapy, summarizes the efficacy and safety of some critical clinical

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trials, and highlights possible combination treatment options in gastric cancer. This manuscript also provides insight into the current research limitations and indicates the development direction for future research of PD-1/PD-L1 checkpoint inhibitors.

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INTRODUCTION

Cancer immunotherapy is one of the most successful therapies in the field of cancer treatment in recent years[1]. Following surgery, radiation, chemotherapy, and targeted therapy, immunotherapy has become a new method for the treatment of cancer. As early as 2013, cancer immunotherapy was rated as one of the top ten scientific breakthroughs[2]. Evading immune destruction is one of the hallmarks of cancer, as illustrated by Hanahan and Weinberg[3]. The concept that the immune system can recognize and control the growth of tumors can be traced back to 1893 when William Coley used live bacteria as an immunostimulant to treat cancer. However, due to its limited clinical efficacy, cancer immunotherapy has been met with moderate enthusiasm. This limited efficacy results from the ability of the tumor cells to avoid being identified and eliminated by the immune system, which allows the tumor cells to be part of the host[4]. Over the past few decades, enormous progress has been made in illuminating how cancer evades the immune system, which in turn provides novel methods to stop cancer immune evasion by eliminating cancer cells. Cancer immunotherapy utilizes the host's natural defense mechanism to enhance antitumor immunity for a stronger antitumor effect. At present, cancer immunotherapy includes adoptive cellular immunotherapy, checkpoint inhibitors, and therapeutic cancer vaccines[5-7]. The immunological checkpoint molecules include programmed cell death-1 (PD-1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). The application of immune checkpoint inhibitors has shown significant antitumor effects on several cancers and has tremendously changed the treatment of melanoma, lung cancer, and kidney cancer. Compared with CTLA-4 inhibitors, checkpoint blockades targeting the PD-1/programmed death ligand-1 (PD-L1) axis have more advantages in efficacy and fewer side effects[8], which allows PD-1/PD-L1 antagonists to be developed into a more promising and efficient approach for anticancer therapy.

Gastric cancer is a malignant cancer of the digestive tract that has serious implications for human health worldwide[9]. According to the recent global statistics, gastric cancer remains a significant cancer globally, and there were more than 1000000 newly diagnosed gastric cancer cases in 2018 along with an estimated 783000 deaths (1 in every 12 deaths globally), making it the fifth most frequently diagnosed cancer and the third leading cause of cancer death[10]. *Helicobacter pylori* is the main risk factor for gastric cancer, with almost 90% of new cases of stomach cancer being ascribed to an infection with *Helicobacter pylori*[11,12]. Due to the lack of specific symptoms and signs in the early stage, most patients are diagnosed with gastric cancer at the advanced stage, which severely affects the prognosis of the patients. Although there are some advances in early gastric cancer screening and treatment, the 5-year survival rate of patients with advanced gastric cancer is still below 10%[13]. Endoscopic resection is a critical method in the treatment of early gastric cancer. The treatment of advanced gastric cancer is usually based on surgery and supplemented by chemotherapy[14]. Combination chemotherapy is the first-line treatment for patients with advanced gastric cancer. Several cytotoxic drugs, such as fluoropyrimidine, platinum, paclitaxel, and irinotecan, have curative effects on gastric cancer. Although tremendous progress has been made in chemotherapy, the overall prognosis is still poor[15]. Furthermore, an increasing number of patients who were initially sensitive to chemotherapy gradually acquired drug resistance during treatment, which limits the further application of chemotherapy drugs. Additionally, targeted therapies against HER2 and VEGFR have also been approved for the treatment of advanced gastric cancer, but the 5-year overall survival (OS) is only 20%-30%[16].

Recently, cancer immunotherapy, especially with checkpoint antagonists, has been transforming the entire field of cancer treatment and has achieved optimistic effects in solid tumors such as melanoma, lung cancer, and kidney cancer. Furthermore,

PubMed and The American Society of Clinical Oncology Annual Meeting data suggest that PD-1/PD-L1 inhibitors may lead us into a new era for the treatment of gastric cancer[16]. Herein, we review the mechanisms of PD-1/PD-L1 blockade therapy, summarize the present knowledge of PD-1/PD-L1 inhibitors to reveal their efficacy and safety in stomach cancer or gastroesophageal junctional cancer, and highlight the possible combination of conventional therapy with PD-1/PD-L1 checkpoint inhibitors.

MECHANISM OF ACTION OF PD-1/PD-L1 BLOCKADE THERAPY

PD-1, a transmembrane receptor on T cells, was initially identified from apoptotic T cell hybridomas through a subtractive method and has become known as a predominant negative regulator of antitumor T cell effector function when engaged by its ligand PD-L1, which is expressed on the surface of cells within tumors[17]. PD-1 bears its name from its earliest description that it was expressed as a receptor involved in cell death[18]. As a significant member of the B7/CD28 costimulatory molecule superfamily, PD-1 is primarily expressed on the surface of activated T and B cells. Both PD-L1 (also known as B7-H1) and PD-L2 (also known as B7-DC) are ligands of PD-1, and they are essential members of the costimulatory molecules in the B7 family[19,20]. PD-L1 is usually expressed in antigen-presenting cells (APCs), such as macrophages and DCs; however, in the presence of inflammatory factors, such as interferon (IFN) or interleukin 4 (IL-4), PD-L1 is also expressed in epithelial and skin cells[21]. PD-L2 has more exclusive expression than PD-L1 in APCs[22,23]. The binding of PD-1 to its ligands functions as an immune checkpoint and regulates the host's costimulatory or inhibitory signals to exert effects on T lymphocytes, thereby modulating the magnitude and duration of T lymphocyte responses.

Under physiological conditions, the combination of PD-1/PD-L1 produces an inhibitory signal to prevent the host from developing autoimmune disease. However, when an inflammatory response occurs in the host, the binding of PD-1 prevents the spread of inflammation, thus localizing tissue damage and preventing the excessive inflammatory reaction. Furthermore, within the background of the tumor microenvironment, antitumor T cells continuously recognize cognate tumor antigens from when cancer develops in the primary stage to the formation of metastatic lesions. Activation of the TCR gives rise to the production of proinflammatory cytokines, including IFN-γ, which is the most potent driver of reactive PD-L1 expression[22,24]. Moreover, the chronic expression of IFN-γ in the microenvironment induces the elevated expression of PD-1 on the infiltrated T cells. The recognition of PD-1 on antitumor T cells by the highly expressed PD-L1 on tumor cells not only inhibits secretion of T cell immune stimulating cytokines (IL-2, IFN-γ, and tumour necrosis factor-α) but also promotes the secretion of the immunosuppressive cytokines (IL-10), thus inhibiting T cell activation and proliferation[25]. Eventually, the tumor cells evade immune destruction. PD-1 is therefore a negative regulator of immune responses and is becoming a promising therapeutic target in cancer immunotherapy.

PD-1/PD-L1 EXPRESSION AND ITS CORRELATION WITH CLINICOPATHOLOGIC FEATURES OR PROGNOSIS IN PATIENTS WITH GASTRIC CANCER

A growing number of studies have been conducted to illuminate the correlation between PD-1/PD-L1 expression and clinicopathologic features or prognosis in patients with gastric cancer. Wang *et al*[26] obtained tissues from 509 patients who underwent gastrectomy, and all tissues were collected and analyzed in the form of a tumor microarray (TMA). In that study, the authors found that a positive PD-L1 status was correlated with high CD3+ and CD8+ T cell invasion. Positive expression of PD-L1 and CD8+ T cells was associated with long OS time in stomach cancer patients, but there were no significant differences noted between the groups with high and low PD-1 and CD3 expression. These results suggest that PD-L1 expression and a high density of CD8+ T cells may serve as prognostic indicators in patients with advanced gastric cancer. Moreover, in a cellular and specimen-based study, Amatatsu *et al*[27] investigated PD-L1 mRNA expression in three gastric cancer cell lines and 124 blood specimens from patients with gastric cancer by qRT-PCR assays. It was demonstrated that a high level of PD-L1 expression significantly correlated with deep

tumor invasion, distant metastasis, and advanced stage (P = 0.001, P < 0.001, and P < 0.001, respectively). In terms of diagnostic performance, surprisingly, the area under the ROC curve for predicting patients with distant metastasis was 0.772. The sensitivity and specificity of PD-L1 mRNA expression for predicting distant metastasis were 0.814 and 0.667, respectively. In addition, compared with patients with low PD-L1 expression, patients with high PD-L1 expression had a significantly lower 5-year survival rate (84.1% *vs* 50.0%, P < 0.0001). Univariate and multivariate analyses of survival revealed that PD-L1 expression was significantly associated with postoperative survival (P < 0.0001) and could be selected as an independent prognostic factor (P = 0.024). Similarly, in a study that involved 465 patients, Böger *et al*[28] reported that the immunohistochemical analysis results of a TMA exhibited a close relationship between the protein expression of PD-L1 and some important prognostic clinicopathological factors, including depth of tumor invasion, distant metastasis, and UICC stage. These findings imply that the assessment of PD-L1 expression has potential clinical application for monitoring tumor properties and progression in patients with stomach cancer. Moreover, the cancer genome atlas (TCGA) classifies gastric cancer into the following four molecular subtypes: (1) Epstein-Barr virus (EBV)-positive; (2) microsatellite instability (MSI); (3) chromosomal instability; and (4) genomically stable[29]. Identification of these subtypes offers a roadmap for patient stratification, and trials of targeted therapies also provide the necessary molecular tools to realize individualized treatment in cancer. A total of 15 eligible studies that included 3291 patients were selected for a meta-analysis[30], which showed that PD-L1 expression was associated with OS in gastric cancer (HR = 1.46, 95%CI: 1.08 ± 1.98; P = 0.01). The authors also found that EBV infection-positive (EBV+) and MSI tumors are more likely to express PD-L1 than the other types of gastric cancer tumors, which is consistent with the results of previous reports[31-34]. This result may provide evidence that gastric cancer patients, especially those with the subtypes of EBV+ and MSI tumors, may be prime candidates for PD-1 blockade therapy. Nevertheless, an original study from Japan showed that EBV-positive gastric cancer cells that express high levels of PD-L1 inhibited T-cell proliferation, and the IFN-γ signaling pathway played an important role in the expression of PD-L1[35].

However, the heterogeneous expression of PD-L1 within primary tumor sites is one of the critical obstacles to the clinical treatment of PD-1/PD-L1 checkpoint blockades[36]. The KEYNOTE-010 study suggested that the level of PD-L1 expression could act as a useful molecular tool to distinguish responders from nonresponders in PD-1/PD-L1 immunotherapy[37]. As mentioned above, the status of PD-L1 expression in blood specimens or tissue specimens is not only associated with clinicopathological features, prognosis, and diagnostic performance but is also associated with the therapeutic effects of PD-1/PD-L1 checkpoint blockades.

CLINICAL EFFECTS OF PD-1/PD-L1 INHIBITORS IN GASTRIC CANCER

PD-1/PD-L1 checkpoint blockades have dramatically transformed the landscape for conventional treatments in patients with gastric cancer. At present, there are five anti-PD-1 or anti-PD-L1 antibodies approved by the FDA for approximately 11 cancer indications[17]; these approved antibodies include two antibodies for PD-1, nivolumab and pembrolizumab, and three antibodies for PD-L1, atezolizumab, avelumab, and durvalumab. These drugs are still in the early stages of clinical research. The current PD-1 inhibitors are mainly used for the treatment of melanoma, non-small-cell lung cancer (NSCLC), and urothelial cancer. Based on the efficacy of PD-1 blockers in NSCLC and melanoma patients, PD-1/PD-L1 inhibitors will hopefully continue to expand their range of applications. Clinical trials with PD-1/PD-L1 antibodies have been initiated in multiple studies. These studies investigated the efficacy and safety of PD-1/PD-L1 antibodies in the treatment of melanoma, urinary tract cancer, digestive tract tumors, and malignant gliomas. Here, we focus on the treatment of gastric or gastroesophageal junctional cancer with PD-1/PD-L1 inhibitors.

The KEYNOTE-012 study[38], a multicenter phase Ib trial using the anti-PD-1 antibody pembrolizumab, included 162 patients with recurrent or metastatic adenocarcinoma of the stomach or gastroesophageal junction cancer. The PD-L1 positive rate in these patients was 40%. All 39 patients were treated with pembrolizumab at 10 mg/kg once every 2 wk for 24 mo, and the endpoints included trial completion (24 mo), complete remission (CR), cancer progression, or the occurrence of unacceptable toxic effects. The results showed that the objective response rate (ORR) was 22.2% (95%CI: 10.1%-39.2%), the rate of grade 3 or 4 treatment-related adverse events (TRAES) was 13%, the median progression-free

survival (PFS) time was 1.9 mo (95%CI: 1.8-3.5), and the median OS time was 11.4 mo. At the six month follow-up, the PFS rate was 24%, the OS rate was 69%, and nearly 53% patients experienced tumor shrinkage to some degree. Moreover, no patients withdrew from the trial due to immune-related adverse reactions. Although this trial did not include a control group, the side effects were still in the acceptable range, and these results warranted further study in phase II and III trials. CheckMate-032[39] was a multicenter phase I/II cohort study that treated advanced gastric cancer patients with nivolumab. This trial enrolled 59 patients diagnosed with advanced and metastatic (A/M) gastric or gastroesophageal junction cancer, and the positive rate of PD-L1 expression in all patients was 38%. All patients were prescribed 3 mg/kg of nivolumab every 2 wk until unacceptable toxicity effects occurred. The results showed that the ORR was 14%, the OS was 5 mo (95%CI: 3.4-12.4), and the 12-mo OS rate was 36%. Moreover, no treatment-related deaths occurred in this study, and all adverse reactions were controllable. The analysis of the classified data demonstrated that the ORRs in the PD-L1-positive and PD-L1-negative patients were 27% and 12%, respectively. Nivolumab had improved efficacy in the PD-L1-positive patients than in the PD-L1-negative patients. In a randomized controlled phase III trial published in *Lancet*, 493 participants were randomized into a nivolumab-treated group and a placebo-treated group. The OS in the two groups was 5.26 mo and 4.14 mo, respectively (HR: 0.63; 95%CI: 0.51-0.78; $P < 0.0001$); in comparison, the OS for the PD-L1-positive patients in the treatment and control groups was 5.22 mo and 3.82 mo, respectively (HR: 0.51; 95%CI: 0.21-1.25). The 12-mo OS rate in the treatment group was significantly higher than that in the control group (26.2% *vs* 10.9%). Although most of these clinical trials did not list positive PD-L1 expression as one of the inclusion criteria, the results did provide solid evidence that, compared with conventional therapy, PD-1/PD-L1 inhibitors brought new hope for gastric cancer patients with highly expressed PD-L1.

The tumor microenvironment is complicated and interacts with multiple signaling pathways, both of which jointly regulate the initiation and progression of cancers and even the responses to specific therapies. Studies have demonstrated that there are a variety of signaling pathways involved in cancer immunotherapy and that these pathways may interact with each other[40]. Acquired resistance after a period of response is one of major problems with checkpoint blockade therapy as well[41]. Therefore, it is often difficult to achieve the desired clinical effects with the long-term application of PD-1/PD-L1 inhibitors or single-agent treatment. To maximize the benefits of cancer therapy, the combination of different immunotherapies or immunotherapy with conventional therapies such as radiotherapy, chemotherapy, and oncogene-targeted therapy, has been shown to alter the immunosuppressive tumor microenvironment and enhance the ability to eliminate cancers, which is the future direction for cancer therapy[42].

A clinical trial was designed based on the foundation of the CTL-4 and PD-1 pathways having coinhibitory roles after preclinical studies showed evidence of synergy in syngeneic mouse models. In this trial, the patients were treated with a combination of ipilimumab and nivolumab to block CTLA-4 and PD-1, respectively[42]. The data showed that in the single treatment group, the time to progression (TTP) was 6.9 mo, and the ORR was 57.6%, while in the combination treatment group, the TTP was 11.5 mo, and the ORR was 57.6%[43]. Furthermore, KEYNOTE-059[44] was a phase II cohort clinical trial that studied pembrolizumab alone or in combination with cisplatin/5-FU among advanced gastric cancer patients. The data showed that the PD-L1 positive rate in the 25 enrolled patients was 64%, the ORR was 60% (95%CI: 38.7~78.9), the ORR of PD-L1-positive patients was 68.8%, the ORR of PD-L1-negative patients was 37.5%, the PFS was 6.6 mo (95%CI: 5.9-10.6), and the OS was 13.8 mo. Despite the fact that there were no adverse events related to death, the rate of grade III-IV TRAES remained high (76%) and included diarrhea, dysgeusia, thyroid disorders, and nausea. Clearly, the coinhibitory group benefitted more than the single inhibitory or traditional therapy group. On the basis of improving safety and efficacy, minimizing the adverse event rate is a major problem that is needed to address in combination treatments.

Several studies have demonstrated that the PD-L1 positive rate in gastric cancer tissues was over 40%[45-47]. We have noted that according to the molecular characteristics of gastric cancer, the TCGA divided stomach cancer into four molecular subtypes in 2014. The EBV-positive type accounts for 9% of all gastric cancers and displays recurrent PIK3CA mutations, extreme DNA hypermethylation, and high expression of PD-L1/2[29]. This classification provides a theoretical basis for the simultaneous treatment of PD-L1 inhibitors and anti-EB virus therapy. Furthermore, CD40 is one of the critical costimulatory molecules in the antitumor treatment immune response, but the effects of CD40 monoclonal antibody from clinical trials were unsatisfactory[48]. One explanation for this phenomenon is that the

expression of PD-L1 on the surface of tumor cells was also elevated with the use of a CD40 agonist. Therefore, when conducting research to illuminate the mechanism of costimulatory molecules, blocking the PD-L1 pathway is of great importance. In addition, numerous studies have revealed that dysregulation of the Wnt/β-catenin signaling pathway occurred in more than 70% of gastric cancer patients[49]. Activation of the Wnt/β-catenin signaling pathway is not only involved in the physiological processes of proliferation, invasion, metastasis, and drug resistance[50-52] but is also negatively correlated with T cell invasion within many tumors such as colorectal cancer[53], melanoma[54], ovarian cancer[55], and prostate cancer[56]. In contrast, the inhibition of the Wnt/β-catenin signaling pathway significantly suppressed proliferation and metastasis both *in vitro* and *in vivo*[57]. These studies suggest that Wnt/β-catenin signaling pathway inhibitors may stimulate immune cells and enhance T cell infiltration in tumors, allowing tumors to respond to immunotherapy. It is apparent that more novel studies are needed to identify potential therapeutic targets to promote the exploration and realization of the potency of combination therapy.

CONCLUSION

Although considerable progress has been made in cancer therapy and the treatment of cancers has entered the new era of immunotherapy, the efficacy and safety of PD-1/PD-L1 inhibitors in advanced gastric cancer patients still need to be further explored by in-depth research in clinical settings. First, most of the clinical trials were primarily limited to early stage I or II disease, and the number of PD-L1-positive patients in the treatment group remained relatively low, which prevents gathering enough direct and potent evidence to validate the curative effects. Second, given the results of the clinical trials up to now, TRAES may become one of the critical factors that thwarts the future application of PD-1/PD-L1 blockade therapy. Identifying and understanding the mechanism of adverse events are of great importance in preventing the occurrence of side effects. Third, after the safety and efficacy of cancer immunotherapy have been validated, the next question is how to select the best treatment method for specific patients. According to the comprehensive molecular characterization of gastric adenocarcinoma, the single-cell sequencing technique would help researchers to recognize different subtypes, discriminate responders, and design the best treatment strategy for patients, allowing individualized cancer therapy to become a reality. Thus, it is essential to list PD-L1-positive gastric cancer patients in the inclusion criteria, minimize the rate of adverse events, and use molecular tools to identify specific patient subpopulations in the research of cancer immunotherapy.

The efficacy of the combination of PD-1/PD-L1 blockade therapy with other traditional therapies remains to be fully elucidated. Combination therapy provides a new direction for research and is a new aspect of cancer immunotherapy. The combination of radiation and anti-PD-1/PD-L1 therapy is as an example of this new area. Ahmed *et al*[58] retrospectively reviewed patients who received stereotactic radiosurgery (SRS) for melanoma brain metastases (BM). The patients were treated with SRS before, during, or after nivolumab therapy. Their results demonstrated that when compared with SRS alone, the combination therapy was better tolerated with no unexpected neurotoxicity. In addition, these patients had superior out-of-field BM control and OS compared with those who received the current standard treatment for melanoma[58]. Although no prospective trials have been published, there are currently several cumulative trials evaluating the safety and efficacy of PD-1/PD-L1 inhibitors combined with radiation therapy in various malignancies[59]. Preliminary reports from some of these trials have shown promising outcomes[60,61]. Consequently, efforts still need to be made in the exploration of combination therapy, new molecular targets, or already identified targets. Based on the recent successes of the field of immunotherapy, continuing to incorporate knowledge from mechanistic basic science research is essential to achieving therapeutic success.

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