Therapeutic Strategy and Resistance Mechanism of PD-L1 Monoclonal Antibody in Precision Population of Gastric Cancer

Dantong Zhao *

Qingdao Medical College of Qingdao University, Qingdao University, Qingdao, Shandong, China

* Corresponding Author Email: zhaodantong@qdu.edu.cn

Abstract. PD-L1 is a core inhibitory immune checkpoint that finely regulates immune homeostasis. PD-L1 is closely linked to the pathogenesis of autoimmune diseases and malignant tumors, especially tumor immune escape, making it a pivotal target for cancer immunotherapy. This paper focuses on the biological functions of this immune checkpoint pathway, how to regulate the progression and metastasis of gastric cancer, and real-world use of PD-L1 monoclonal antibodies as well as their resistance mechanisms and safety profiles. Atezolizumab combined with chemotherapy or trastuzumab-based targeted therapy significantly improves the pathological complete response rate in gastric cancer patients. PD-L1 CPS ⩾5 is an indicator used to judge the therapeutic effect. Durvalumab exhibits robust therapeutic benefits in neoadjuvant/adjuvant therapy, second-line treatment, and maintenance therapy for advanced gastric cancer, particularly in patients with high PD-L1 expression. Therapeutic resistance to PD-L1 inhibitors involves multiple factors including T-cell exhaustion, myeloid cell infiltration, exosomal PD-L1 secretion, and post-translational modifications of PD-L1. Immune-mediated toxicities arising from PD-L1 inhibitor therapy are manageable and not correlated with PD-L1 expression levels. This paper comprehensively summarizes the advances in PD-L1-targeted immunotherapy for gastric cancer, providing valuable insights for optimizing clinical treatment strategies and exploring novel solutions to overcome drug resistance.

Keywords: Gastric cancer; PD-L1; tumor immunotherapy; ICI; CPS.

1. Introduction

Gastric cancer (GC) is a is a disease with a high incidence and mortality. Surgery has always been the only curative treatment for GC, but most GC cases will progress to the advanced stage at the initial diagnosis. Thus, the treatment situation is not optimistic. Over the recent period, immunotherapy dramatically changed the treatment landscape of gastric cancer [1]. Immunotherapy is a method of treating disease primarily by regulating or enhancing the patient's own immune system's ability to fight the disease. At present, immunotherapy has shown its remarkable efficacy in treating many diseases. For the treatment of malignancies, immunotherapy refers to a series of treatment strategies that exploit the host immune machinery for tumor detection, assault, and removal.

In recent years, immunotherapy has become an important therapeutic strategy for gastric cancer, especially advanced gastric cancer. Compared with the classic surgery, cytotoxic chemotherapy and radiotherapy, immunotherapy can break through the limitations of traditional treatment methods, transcend them, and better efficacy to gastric cancer patients. Currently, adoptive cell therapy (ACT), cancer vaccines, and immune checkpoint inhibitors (ICI) are all essential components of immunotherapy for gastric cancer [2]. Among them, ICI shows promising therapeutic potential in clinical gastric cancer treatment applications. The Programmed Death-1 (PD-1) receptor and its ligand PD-L1 constitute an immune checkpoint pair, and modulate immune activation. PD-L1 stands out for its abundant presence on diverse solid tumors. PD-1–PD-L1 binding safeguards immune homeostasis by dynamically regulating immune responses. PD-L1 can regulate immune homeostasis by binding to PD-1. To prevent the excessive activation of molecular signal transduction pathways, PD-1/PD-L1 is dynamically controlled under strict supervision [3]. PD-L1 monoclonal antibody is a type of immune checkpoint inhibitor that can block its binding to PD-1. Combined Positive Score

(CPS) is considered to reflect how densely the immune biomarker PD-L1 is displayed. CPS is commonly used to predict the ICB therapeutic yield in gastric cancer. To date, the predictive value of CPS in gastric cancer immunotherapy has been confirmed by Phase III clinical trials, but remains accumulating support from clinical data [4]. This paper analysis the latest advances in the mechanisms of action, treatment strategy, resistance mechanism and safety profiles of anti-PD-L1 mAb in the field of the target population for precision therapy of gastric cancer (CPS≥5), aiming to evaluate the advantages, disadvantages, and application value of anti-PD-L1 mAb.

2. PD-L1-Involved Signaling Pathway

The PD-1 receptor and its ligands constitute a major class of inhibitory immune checkpoint proteins. PD-1 expression is observed on diverse immune cell types. The PD-L1 ligand is primarily expressed on immune cells capable of antigen presentation and tumor cells [4]. The primary function of PD-1 is the negative regulation of immunity, mediated by its interaction with specific ligands. After the PD-1–PD-L1 ligand–receptor signaling chain is activated, it sends a signal that inhibits the activity of T cells. This pathway not only prevents immune disorders, but also prevents harmful immune responses and prevents immune dysregulation. PD-1/PD-L1 prevents normal tissues from experiencing inflammatory responses and reduce the occurrence of immune-mediated diseases. The immune system strictly and dynamically regulates this axis due to the importance of its function. The checkpoint is involved in the pathology of various immune-mediated diseases [5].

PD-L1 is often upregulated by tumor cells, and modulates the activity of its resident signal transduction pathway through specific signal transmission. PD-L1 engages PD-1 on T-cell membranes, and can lead to T cell dysfunction or even T cell exhaustion. Therefore, tumor cells can escape the cytotoxic effects mediated by cytotoxic T cells by overexpressing PD-L1. After T-cell exhaustion, tumor cells can become more invasive and secrete pro-inflammatory cytokines (IL-10 and others) to foster a pro-inflammatory environment. Then, tumor cells in the pro-inflammatory environment are more likely to survive and are more likely to grow, spread, and metastasize.

PD-L1 is not only very critical in the occurrence and growth of tumors, but also affects each step of tumor metastasis. Detachment of tumor cells from the primary focus is a prerequisite for metastasis, and this biological process is driven by the induction of epithelial-mesenchymal transition (EMT) via PD-L1. After tumor cells enter the circulation, they acquire the ability to make immune cells ignore them by overexpressing PD-L1. Then CTCs can survive and metastasize to distant sites better. During the process of tumor cells reaching the colonization site and colonizing it, PD-1/PD-L1 is further activated to form a more inhibitory microenvironment to facilitate the progression of metastasis. These mechanisms inspire the research on cancer treatment.

3. PD-L1 Monoclonal Antibody for Gastric Cancer

3.1. Atezolizumab

Atezolizumab is the first drug approved by the FDA for PD-L1 blockade. It has been approved for marketing in multiple countries including China. Its established indications cover many cancers. Evidence of clinical activity was seen across multiple tumor types, with efficacy demonstrated in many cancers including non-small cell lung cancer (NSCLC). Atezolizumab has shown high-level antitumor activity in various malignant tumors, improving patients' therapeutic benefit. The efficacy has been confirmed through researchs[6].

In an initial Phase Ib trial, patients with CPS≥5 who received atezolizumab combined with chemotherapy experienced a markedly prolongs life expectancy. In the PD-L1 high-expression subgroup, atezolizumab is likely to increase the efficacy of chemotherapy through a similar mechanism. Targeted combination immunotherapy for gastric cancer is being explored. The NCT04661150 trial is a multicenter, randomized, open-label phase II clinical study [7]. This study is designed to investigate whether the combination of atezolizumab and trastuzumab with XELOX

chemotherapy is effective and safe. It represents a new therapeutic option for gastric/gastroesophageal junction adenocarcinoma (GEJA) characterized by HER2 positivity.

Forty-two patients were randomly assigned to Group A and B (1:1). 21 patients assigned to Group A received treatment with atezolizumab plus trastuzumab plus capecitabine and oxaliplatin chemotherapy regimen (XELOX). An additional 21 individuals allocated to Group B received treatment with trastuzumab plus XELO. For these patients, this combination therapy improved their pathological complete response (pCR) rate (that is, the predefined primary endpoint). Favorable tolerability was also observed with this combination therapy protocol. By analyzing the consistency of detection of 22C3 pharmDx and 28-8 pharmDx, the conclusion can be made that the subgroup with CPS $\geq$ 5 in gastric cancer onstrates increased responsiveness to immunotherapy. PD-L1 CPS can be an indicator for screening the population who can better benefit from immunotherapy.

3.2. Durvalumab

As a standard therapy, FLOT shows favorable therapeutic efficacy. But there is a high recurrence rate among patients. NCT04592913 is a phase 3, multinational, double-blind, randomized trial with event-free survival (EFS) designated the primary survival benchmark. A total of 800 eligible patients were randomized to two equal groups (n=400 per group), namely the durvalumab arm and the placebo arm. Durvalumab group received durvalumab plus FLOT, while the placebo group received FLOT alone. The results show that the durvalumab group had a higher EFS, and the intergroup difference was 8.9% ($P < 0.001$). As secondary outcomes, durvalumab plus FLOT was also significantly superior to FLOT alone in OS and pCR. Patients with PD-L1 CPS of 5 or higher derive a more pronounced survival advantage from this regimen [8]. Further evidence supports the use of durvalumab as a neoadjuvant agent; when added to the DOS regimen, it improved outcomes in patients with resectable locally advanced gastric cancer.

In metastatic gastric cancer, durvalumab combined with tremelimumab (CTLA-4 inhibitor) and paclitaxel is used as a second-line regimen. NCT03751761 is a multicenter phase Ib/II study. In the phase II segment, the primary efficacy measure was defined as the objective response rate (ORR). In biomarker-selected patients (CPS≥5), this regimen achieved an ORR of 23%, PFS of 2.7 months, and OS of 8.7 months, confirming its efficacy as second-line therapy [9]. If the patients are stable after first-line chemotherapy, durvalumab maintenance therapy can prolong PFS (HR 0.45), especially in those with CPS≥5[10]. This finding supports durvalumab maintenance therapy as a promising option for these patients.

4. Drug Resistance Mechanism

4.1. Tumor Microenvironment (TME)

PD-L1 resistance often reduces the effectiveness of long-term treatment. The resistance mechanism of PD-L1 is very complex and still needs to be verified in terms of clinical translation. Resistance to PD-L1 monoclonal antibodies can be considered from the following aspects. Cytotoxic T cells mediate anti-tumor immunotherapy by directly killing cancer cells, but various inhibitory factors in the TME accelerate T-cell exhaustion. When cytotoxic T cells are exhausted, the therapeutic effect of anti-tumor immunotherapy is affected regardless of PD-L1 expression level. Combining PD-L1 monoclonal antibodies with IL-2 can reverse T-cell exhaustion and improve efficacy, with related clinical trials ongoing [11]. Common myeloid progenitors (CMPs) in bone marrow differentiate into different immune cells such as granulocytes, monocytes, and macrophages during development. These cells are collectively called a myeloid cell. Myeloid cells serve as a key determinant in body immunity, maintenance of tissue homeostasis, hematopoietic function.

In TME, myeloid cells can secrete TGF-β. The TGF-β-related pathway mediates immunosuppression through two mechanisms: suppressing T cell effector molecules and upregulate the density of PD-L1 on tumer cells. By virtue of synergy, this effect leads to a compounded inhibition

of immune cell activity. The resulting immunosuppression culminates in treatment resistance. Tumor-derived lactic acid metabolites acidify the TME through MCT-1 transport, making it difficult for PD-L1 to bind to anti-PD-L1 and causing resistance. Inhibiting MCT-1 can reduce TME lactic acid concentration and reverse this resistance, with MCT-1 inhibitors in phase I clinical trials.

4.2. Tumor Cell Characteristics

Exosomes released by tumor cells carry PD-L1. This exosomal PD-L1 can enter the circulation system and bind to peripheral T cells at a distance, thereby suppressing systemic anti-tumor immunity. If PD-L1 blockers only work in the tumor microenvironment, they cannot completely block this immune checkpoint pathway. Exosomal PD-L1-mediated immunosuppression poses a major limitation to the clinical benefit from immunotherapy. It is also one of the important mechanisms of drug resistance [12].

Carnitine palmitoyltransferase 1A (CPT1A), a key enzyme in fatty acid metabolism and a succinyltransferase, succinylates PD-L1 to regulate its stability. CPT1A affects antigen presentation and PD-L1 expression through different pathways; inhibition of CPT1A reduces PD-L1 succinylation, upregulates PD-L1 expression, and leads to resistance. PD-L1 glycosylation is a form of post-translational modification. This process enhances its binding affinity with PD-1, thus forming a more stable and longer-lasting receptor-ligand complex, thereby driving immune escape [13].

4.3. Signal Strength

Multiple intrinsic and extrinsic factors converge to regulate PD-L1 synthesis. TRAF6 is one such regulatory molecule. Mechanistically, it acts by participating in the TRAF6-YAP1/TFCP2 pathway. This mechanism regulates PD-L1 internally and points to previously unknown resistance routes [14]. Additionally, PD-L1 is present on tumor-derived extracellular vesicles (TEVs). These TEVs can act as decoys, efficiently binding to anti-PD-L1 (αPD-L1) antibodies. The antibody-bound TEVs are then readily phagocytosed and degraded by macrophages, sequestering a substantial amount of αPD-L1. This consumption preempts antibody resources, leading to insufficient tumor PD-L1 blockade and contributing to resistance. Beyond PD-L1 expression-related factors, neoplastic cells may upregulate other immune checkpoint molecules (e.g., CTLA-4, LAG-3) on their surface after anti-PD-L1 agents take effect. This is intended for evading immune surveillance. Combining PD-L1 monoclonal antibodies with other antibodies can prevent this compensatory activation and improve efficacy [15].

5. Adverse Reactions

No studies have shown that PD-L1 levels correlate with adverse-event intensity. There was no difference in the CTCAE grade ≥3 event frequency between gastric cancer populations with CPS ≥ 5 and CPS < 5. Therefore, immune-related adverse events (irAEs) commonly observed in the therapeutic blockade using PD-1/PD-L1-directed monoclonals. It is also an issue that needs attention in clinical work.

5.1. The Dominant Mechanistic Route

PD-L1 is also extensively present in non-malignant sites. PD-L1 mAb also block the expression pathways of normal cells, like vascular endothelial and immune cells. Inhibition of normal expression may affect the body's autoimmune function and even cause tissue damage. Despite receiving the same treatment, every patient responds differently to medications. In some cases, among patients with a BMI ≥ 30 kg/m², patients taking PD-L1 inhibitors, patients with pre-existing autoimmune diseases, and patients taking salicylates during the study, are considered more susceptible to irAEs.

5.2. Immune-Related Toxicity

Immune-related toxicity limits the clinical application of immune checkpoint antibodies (targeting PD-1 or PD-L1). These agents relieve PD-1/PD-L1–dependent T-cell paralysis through checkpoint

antagonism. But they may also trigger immune overreaction. Though systemic toxicity incidence is low, consequences are severe if it occurs. Frequently observed irAEs are cutaneous, with spontaneous skin diseases reported in checkpoint inhibitor treatment. For patients with autoantibodies but no active autoimmune disease, PD-L1 antibodies are safe, but antithyroid antibody-positive patients have a 5%-10% higher thyroid dysfunction risk, thus, pre-treatment thyroid antibody testing and during-treatment function monitoring are needed.

No studies link PD-L1 antibodies to pulmonary toxicity in gastric cancer, but interstitial pneumonia is a severe and recognized risk in NSCLC, reflecting that pneumonitis is a class-effect toxicity of ICIs. Heart-targeted autoimmunity causes immune-related myocarditis: cardiac irAE incidence is 3.1% with ICI monotherapies, and dual ICI therapies have higher cardiotoxicity. ICI-induced colitis presents with diarrhea, prompting medical attention. Additionally, some toxicities persist as chronic irAEs, and even with treatment discontinuation and immunosuppressants, these long-term effects are hard to alleviate.

6. Conclusion

The study on ICIs is a hot topic in the exploration of malignant tumor treatment, which can provide important guiding value for clinical practice. PD-L1 mAbs has shown clinical value in gastric cancer patients with CPS≥5, some PD-L1 monoclonal antibodies are being studied in clinical research. Research on the resistant mechanism and the occurrence of adverse reactions of the PD-L1-targeting agents is also ongoing. The release of these research results can provide more new treatment strategies and options for patients with CPS≥5, and improve the quality of their lives. At the same time, it is also facing many problems and challenges. In terms of clinical application, controversy still exists regarding whether the CPS score can be used as a predictive indicator. Because when different inspection methods are used, there are differences in the positive rates that can be detected. This difference can even reach 2 times. In order to evaluate the efficacy of drugs more objectively, it is necessary to further verify whether CPS≥5 as a screening criterion is universal in the future, and adopt unified standards for CPS testing. The biopsy samples used for detection cannot fully and comprehensively reflect the changes in PD-L1 protein density in TME. In clinical practice, doctors need more advanced technologies to dynamically monitor the TME to adjust treatment plans in a timely manner. Immunotherapy exhibits higher toxicity in patients with CPS ≥ 5, which may limit the long-term deployment of anti–PD-L1 biologics. Optimizing the safety of this inhibitor monotherapy represents an unmet need, calling for continued clinical investigation. The antitumor efficacy could be maintained or enhanced via targeted delivery, combination therapy with other agents, engineering or optimization of antibody fragments, etc. Some patients with CPS ≥ 5 have primary or acquired resistance, and resistance to PD-L1 mAb is a challenging area of research. Although PD-L1 inhibitors has its limitations, as more in-depth research continues, there is reason to believe that PD-L1 monoclonal antibodies will certainly achieve greater breakthroughs in the treatment of a precision population of gastric cancer with CPS≥5, bringing hope to a large number of patients' lives.

References

[1] WenLong G, Ye H, RuiHua X. Gastric cancer treatment: recent progress and future perspectives. [J]. Journal of hematology & oncology,2023,16(1):57-57.

[2] Santos M, Martins D, Mendes F. Immunotherapy in gastric cancer-A systematic review. [J]. Oncology research, 2025, 33(2): 263-281.

[3] Gao M, Shi J, Xiao X, et al. PD-1 regulation in immune homeostasis and immunotherapy. [J]. Cancer letters, 2024, 588216726-216726.

[4] Zhang X, Dai X, Liu A, et al. Efficacy, safety, and biomarker analysis of first-line immune checkpoint inhibitors with chemotherapy versus chemotherapy for advanced gastric cancer: a multicenter, retrospective cohort study. [J]. BMC medicine, 2024, 22(1): 585.

[5] Xin L, Kuan K, Pan C, et al. Regulatory mechanisms of PD-1/PD-L1 in cancers [J]. Molecular Cancer, 2024, 23(1): 108-108.

[6] ZHAO Tian, LI Zicai, HUANG Lu. Patent Layout and Analysis of Atezolizumab [J]. Chinese Journal of Pharmaceuticals, 2024, 55(10): 1350-1358.

[7] Zhi P, Xiaotian Z, Han L, et al. Atezolizumab and Trastuzumab Plus Chemotherapy for ERBB2-Positive Locally Advanced Resectable Gastric Cancer: A Randomized Clinical Trial [J]. JAMA Oncology, 2025.

[8] Janjigian Y Y, Batran A E S, Wainberg A Z, et al. Perioperative Durvalumab in Gastric and Gastroesophageal Junction Cancer. [J]. The New England journal of medicine, 2025.

[9] Lee W K, Zang Y D, Kim D H, et al. Correction: Multicenter phase Ib/II study of second-line durvalumab and tremelimumab in combination with paclitaxel in patients with biomarker-selected metastatic gastric cancer [J]. British Journal of Cancer, 2025, 133(2): 1-1.

[10] Fong C, Patel B, Peckitt C, et al.Maintenance durvalumab after first-line chemotherapy in patients with HER2-negative advanced oesophago-gastric adenocarcinoma: results from the randomised PLATFORM study. [J]. ESMO open, 2024, 9(7): 103622.

[11] Luo D, Zhou J, Ruan S, et al. Overcoming immunotherapy resistance in gastric cancer: insights into mechanisms and emerging strategies. [J]. Cell death & disease, 2025, 16(1): 75.

[12] Sun G J, Gao Y, Gao S Y, et al. Identification of the exosomal PD-L1 inhibitor to promote the PD-1 targeting therapy of gastric cancer. [J]. European journal of medicinal chemistry, 2024, 268116182-116182.

[13] LEE T A, TSAI E Y, LIU S H, et al. Regulation of PD-L1 glycosylation and advances in cancer immunotherapy [J]. Cancer Letters, 2025, 612: 217498.

[14] Wang L, Liu X, Han Y, et al. TRAF6 enhances PD-L1 expression through YAP1-TFCP2 signaling in melanoma. [J]. Cancer letters, 2024, 590216861-216861.

[15] Gavgani R E, Majidazar R, Lotfinejad P, et al.Immune Checkpoint Molecules: A Review on Pathways and Immunotherapy Implications.[J].Immunity, inflammation and disease, 2025, 13(4): e70196.