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EDITORIAL

Immunotherapy for metastatic gastric cancer

Chang-Fei Li, Li-Li Lian, Qiu-Ru Li, Yan Jiao

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Abstract

This editorial discusses the article written by Chen *et al* that was published in the latest edition of the *World Journal of Gastrointestinal Surgery*. The current study found that programmed cell death 1 ligand 1 (PD-L1) expression is considered as one of the pan-cancer biomarkers of immune checkpoint inhibitors (ICIs) treatment response. Four molecular subtypes are widely used to guide and evaluate the prognosis and diagnosis and treatment of gastric cancer (GC) patients. Clinical trials of ICI treatment including Nivolumab, Pembrolizumab, Avelumab have been conducted for metastatic GC (mGC). The effects of various single agent ICIs on mGC therapy varied. ICIs combined with chemotherapy can indeed bring survival benefits to patients with mGC. Combining ICIs with chemotherapy can give more patients the chance of surgery in the treatment of GC transformation. However, not all PD-L1 positive patients can benefit from it. It is urgent to find better biomarkers to predict the response of ICIs for more precise clinical treatment.

Key Words: Immunotherapy; Metastatic; Gastric cancer; Combined therapy; Programmed cell death 1 ligand 1

Core Tip: The efficacy of different single agent immune checkpoint inhibitors (ICIs) in metastatic gastric cancer (mGC) treatment varies. ICIs combined with chemotherapy can indeed bring survival benefits to patients with mGC. In the future study, more biomarkers should be explored to clinically evaluate the response of ICI treatment to mGC treatment.

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INTRODUCTION

Gastric cancer (GC) is a common digestive tract cancer, with a high incidence and mortality, especially in east Asia[1]. According to the latest data from the national cancer center of China, the incidence and mortality of GC ranked third, posing a severe threat to public health[2]. Despite of advances in the diagnosis and treatment of early GC, more than 50% of GC patients are locally advanced at first diagnosis, with a poor prognosis[3]. Even if these patients received chemotherapy and targeted therapy, the 5-year overall survival (OS) rate of advanced GC worldwide is just 10% to 15% [4]. Particularly, the prognosis for patients with metastatic GC (mGC) is even worse[5].

Programmed cell death 1 ligand 1 (PD-L1) is one of two ligands for the PD-1 receptor. The expression of PD-L1 in tumors is a sign that the anti-tumor activity of the immune system is inhibited. The interaction of PD-1/PD-L1 prevents the activation, cytokine production and cytolytic activity of T lymphocytes, resulting in downregulation or failure of T lymphocyte function[6]. Infiltrating immune cells and tumor cells can both express PD-L1. The current study found that PD-L1 expression is considered as one of the pan-cancer biomarkers of immune checkpoint inhibitors (ICIs) treatment response, and the combined positive score (CPS) and tumor proportion score are utilized as PD-L1 grading standards, which vary among cancer species.

MOLECULAR SUBTYPE

In 2014, the cancer genome atlas research proposed four conventional molecular subtypes of GC: EB virus (EBV), microsatellite instability (MSI), chromosomal instability (CIN) and genomically stability (GS), which are widely used in clinic to guide and evaluate the prognosis and diagnosis and treatment of GC patients[7]. Each subtype has its own unique characteristics. EBV positive GC is mostly poorly differentiated, with high expression of PD-L1[8]. MSI-high (MSI-H) GC shows high mutation rate and hypermethylation, which results in increased production of neoantigen. Moreover, MSI-H GC patients have high infiltration of cluster of differentiation 8^+ T cells in their tumors, which could be attributed to the recognition of a large number of neoantigens and the high expression of corresponding immune checkpoints, such as PD-L1 in the tumor microenvironment[9]. CIN tumors often occur in the gastroesophageal junction with *TP53* repeated mutations[10]. GS tumors usually show diffuse histology and are enriched for mutations of *CDH1* and *RhoA* or *cldn18*-arhgap fusion. In addition, transcriptomic analysis showed that compared with GS or CIN subtypes, the immune cell signaling pathways of EBV positive or MSI-H subtypes were significantly upregulated[11]. These mechanisms suggest that some subtypes of mGC with greater heterogeneity may be more sensitive to ICIs treatment, such as EBV positive and MSI-H subtypes, providing theoretical support for subsequent clinical research.

ICI TREATMENT

Similar to other malignant tumors, the layout of clinical research on ICI treatment of mGC is also gradually developed from third-line, second-line to first-line, from single drug to combination. Several notable clinical trials of ICI treatment for mGC are listed in Table 1.

In the clinical study of attraction-2, anti-PD-1 mAb nivolumab significantly improved the OS of mGC patients who had received second-line or more chemotherapy[12]. Of note, the improved 1.12 months may bring only limited significance in practice. At the same time, nivolumab also significantly improved progression-free survival (PFS) of 0.16 months. In addition, objective response rate (ORR) was also significantly improved ($P < 0.0001$). This study demonstrates that nivolumab not only improves the prognosis of patients with mGC, but it is also extremely safe. As a result, it establishes nivolumab as a third-line treatment in Asian countries and regions.

Pembrolizumab, another anti-PD-1 monoclonal antibody, showed an ORR of 11.6% in patients with mGC treated in the third line or later line in the phase II keynote-059 clinical study[13]. By detecting the expression of PD-L1, researchers found that the ORR value of patients with PD-L1 positive (CPS 1) was 15.5%, while that of patients with CPS ≤ 1 was only 6.4%. This suggests that PD-L1 could be a biomarker for predicting response to pembrolizumab treatment.

Unfortunately, the phase III JAVELIN Gastric 300 clinical study carried out worldwide, showed that the anti-PD-L1 antibody avelumab failed to show an improvement in OS and PFS, when compared to the researchers' choice of

Table 1 Clinical trials of immune checkpoint inhibitor treatment for metastatic gastric cancer

Clinical trial	Treatment	Phase
Attraction-2	Nivolumab	III
Keynote-059	Pembrolizumab	II
JAVELIN Gastric 300	Avelumab	III
Keynote-062	Pembrolizumab combined with chemotherapy	III
Checkmate-649	Nivolumab combined with chemotherapy	III
Attraction-4	Nivolumab combined with chemotherapy	III
Keynote-811	Pembrolizumab combined with trastuzumab and chemotherapy	III

chemotherapy drugs for the third-line treatment of mGC patients, with OS of 4.6 months and 5.0 months [hazard ratio (HR) = 1.1, 95% confidence interval (CI): 0.9-1.4, $P = 0.81$), and PFS of 1.4 months and 2.7 months (HR = 1.73, 95% Cl: 1.4-2.2, $P > 0.99$)[14]. The researchers may have misjudged the efficiency of chemotherapeutic medications in third-line treatment, or prior trials have shown that some mGC will advance rapidly when treated with immunotherapy.

The effects of different single agent ICIs in mGC treatment vary, most likely due to the significant heterogeneity of mGC. Although some biomarkers can predict the response of ICIs treatment in clinic, the value of different drugs varies, so it is urgent to find better biomarkers to predict the response of ICIs to screen the dominant population of different ICIs drugs, guide clinical medication, and make clinical treatment more precise.

ICI COMBINED TREATMENT

In keynote-062 clinical study, compared with chemotherapy alone, chemotherapy combined with pembrolizumab failed to show the benefit of OS and PFS in PD-L1 CPS ≥ 1 and CPS ≥ 10 populations, but it was found that in PD-L1 CPS ≥ 1 population, pembrolizumab combined with chemotherapy group had a higher ORR (49% *vs* 37%)[15].

In the phase III clinical study of global checkmate-649, compared with chemotherapy alone (CapeOX or FOLFOX), nivolumab combined with chemotherapy in the treatment of mGC patients with PD-L1 CPS ≥ 5 reached the primary double endpoint of the study, with median OS of 14.4 and 11.1 months (HR = 0.70, $P < 0.0001$) and PFS of 7.7 and 6.0 months (HR = 0.68, $P < 0.0001$), respectively[16]. In the population with PD-L1 CPS ≥ 1 and all randomized populations, the OS of nivolumab combined with chemotherapy group was beneficial. In addition, in the PD-L1 CPS ≥ 5 population, the ORR obtained by patients receiving nivolumab combined with chemotherapy was significantly higher than that of patients receiving chemotherapy alone (60% *vs* 45%). This clinical study established the position of nivolumab combined with chemotherapy in mGC and accelerated the approval of clinical indications.

At the same time, in the phase III clinical study of Attraction-4 in Asian countries, compared with chemotherapy alone, the combination of nivolumab with chemotherapy (SOX or CapeOX) improved PFS and ORR of patients without PD-L1 screening of mGC patients, with median PFS of 10.45 months and 8.34 months respectively (HR = 0.68, $P = 0.0007$)[17]. Additionally, the ORR was 58% and 48%, respectively, but it did not improve the OS of patients, which may be related to more patients in the chemotherapy alone group received ICIs treatment in the posterior line.

ICIs combined with chemotherapy can indeed bring survival benefits to patients with mGC. Although each drug has a distinct value for survival improvement, it can improve ORR without exception, which indicates that in the future, ICIs combined with chemotherapy strategy can give more patients the chance of surgery in the treatment of GC transformation. However, not all PD-L1 positive patients can benefit from it. It is still necessary to identify new biomarkers to predict the response rate of ICI treatment combined with chemotherapy, as well as screen the dominant population for treatment.

Trastuzumab was found to improve human epidermal growth factor receptor-2 (HER-2) internalization, upregulate PD-L1 expression, and induce lymphocyte expression infiltrated in tumor[18]. A phase III keynote-811 clinical study of pembrolizumab combined with trastuzumab and chemotherapy in the first-line treatment of HER-2-positive mGC patients showed that compared with the placebo group, the pembrolizumab group significantly increased the ORR by 22.7% with higher complete remission (11.3% *vs* 3.1%)[19].

CLINICAL IMPLICATIONS

Although ICI treatment has made significant progress in mGC, it is worth noting that not all patients will benefit from it. The identification of those who can benefit from ICI treatment is the driving force and focus of ongoing research. Existing research has indicated that various biological markers can assist screen the benefit population for optimal ICI treatment, but there are still some limitations. In the future, more biomarkers should be explored to clinically evaluate the responsiveness of ICI treatment to mGC treatment[20].

CONCLUSION

There are four widely utilized molecular subtypes, including EBV, MSI, CIN and GS, to guide and evaluate the prognosis and diagnosis and treatment of GC patients. The **c**linical trials of ICI treatment including Nivolumab, Pembrolizumab, Avelumab have been conducted for mGC. The effects of various single agent ICIs on mGC therapy varied. ICIs combined with chemotherapy strategy can give more patients the chance of surgery in the treatment of GC transformation. However, not all PD-L1 positive patients can benefit from it. It is urgent to find better biomarkers to predict the response of ICIs for more precise clinical treatment.

FOOTNOTES

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