ASIA-PACIFIC JOURNAL OF ONCOLOGY

OPEN ACCESS

REVIEW ARTICLE

Received 22 Feb 2024 | Accepted 07 Mar 2024 | Published Online 08 Mar 2024 https://doi.org/10.32948/ajo.2024.03.01

Research progress of perioperative immunotherapy for locally advanced gastric cancer

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Cite this article: Ma SB, Zhang W, Guo XD, Chen YH, Zhao ZY, Jiang HB: Research progress of perioperative immunotherapy for locally advanced gastric cancer. Asia Pac J Oncol 2024, 5: 1-8. https://doi.org/10.32948/ajo.2024.03.01

Abstract

Gastric cancer is a highly heterogeneous disease, and its occurrence and development are the result of genetic factors, environmental factors, and host factors. As one of the main types of cancer in China, radical gastrectomy is the only chance for patients to be cured, but only 50% to 60% of initially diagnosed gastric cancer patients are suitable for radical gastrectomy, especially in locally advanced and advanced patients. The results of MAGIC and ACCORD07/FFCD9703 confirm the status of combination chemotherapy with fluorouracil as the standard of perioperative treatment for locally advanced gastric cancer. Gastric cancer is one of the most common diseases in China, with high heterogeneity and poor prognosis. Immunotherapy has always been a difficulty in medical research. However, the 5-year overall survival rate for gastric cancer patients remains low. Immunotherapy is effective in the first-line treatment of advanced gastric cancer. At the same time, immunotherapies such as immune checkpoint inhibitors, tumor vaccines, and cell therapy also show certain safety and effectiveness in the perioperative treatment of locally advanced gastric cancer patients. This paper reviews the research progress of immunotherapy in the perioperative treatment of locally advanced gastric cancer.

Key words locally advanced gastric cancer, perioperative period, immunotherapy, neoadjuvant therapy, conversion therapy, tumor vaccine, cell therapy

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Introduction

Gastric cancer is one of the most common malignant tumors of the digestive tract, and its morbidity is among the top 5 in the world, and its mortality is ranked fourth [1, 2]. The global incidence varies by region; East Asia has the highest incidence area of stomach cancer, and about 70% of new cases come from China, Japan, and South Korea every year. Japan and South Korea have successively carried out national gastric cancer screening programs, which led to its detection in the early stage, thereby reducing its mortality rate [3]. Due to the lack of suitable national screening strategies in China, most patients present with either an intermediate or late stages at the time of diagnosis for which the prognosis is often poor [4]. The incidence in Northern Europe and North America is similar to that in Africa and is generally low. It is worth noting that in recent years, the incidence of gastric cancer in young people (<50 years of age) has gradually increased in both low - and high-risk countries. The 5-year survival rate of early gastric cancer is higher, which can exceed 90%. However, due to the hidden onset and rapid progression of gastric cancer, most patients are already in the advanced stage at the time of initial diagnosis and have a poor prognosis. For such patients, the traditional treatment based on chemical therapy (referred to as "chemotherapy") has limited efficacy. According to the RAINBOW Asia trial, the median overall survival of patients with chemotherapy alone is only 7.9 months [5]. That's less than half the median overall survival of today's emerging chemotherapy combined with immunotherapy. This suggests that immunotherapy combined with chemotherapy can improve the overall survival of patients with advanced gastric cancer. Gastric cancer is associated with Helicobacter pylori infection, genetic risk factors, and lifestyle factors [6-9]. Surgery is the only chance to cure gastric cancer patients. However, only 50%-60% of newly diagnosed gastric cancer patients are suitable for radical gastrectomy, and the 5-year survival rate of patients with simple surgery is no more than 30%, especially those with locally advanced and advanced stages often lose the opportunity for surgery [10, 11]. The 5-year survival rates of patients with stage Ⅲ A, Ⅲ B and Ⅲ C were only 30.5%, 20.1% and 8.3%, respectively [12]. Formulating the strategies to improve the resection rate of local advanced gastric cancer patients and to prolong the postoperative survival time is the need of the hour. To improve the prognosis of gastric cancer, researchers have paid more attention to the effectiveness of multimodal therapy, and developed concepts of perioperative treatment such as postoperative adjuvant therapy, neoadjuvant therapy, and conversion therapy [13-15]. Two large randomized clinical trials, MAGIC and ACCORD07/FFCD9703, confirmed fluorouracil-based combination chemotherapy regimen as the standard for perioperative treatment of locally advanced gastric cancer [11, 16]. These two trials have changed the treatment landscape for locally advanced gastric cancer, supporting the use of preoperative chemotherapy + surgery + adjuvant chemotherapy treatment model. However, 5-year overall survival remains low, 67% for patients with localized disease, and 31% for patients with regional spread [17]. Therefore, new combination therapy is needed to improve the therapeutic effect of patients with locally advanced gastric cancer. Immune checkpoint inhibitors, Immunotherapies such as ICIs, tumor vaccine, and cell therapy have shown certain safety and effectiveness in perioperative treatment of locally advanced gastric cancer patients. This article reviews the application of immunotherapy in the perioperative treatment of local advanced gastric cancer, providing ideas for further exploration of the perioperative treatment of local advanced gastric cancer.

Immune checkpoint inhibitors (ICIs)

The application of immunotherapy in gastric cancer includes tumor vaccine, cell therapy, and ICIs, among which ICIs are the most common and the most widely used in gastric cancer with the most noteworthy effect. ICIs have carried out many clinical trials and achieved phased results in the perioperative treatment of locally advanced gastric cancer. Since its introduction, ICIs have shown promising results in patients with melanoma and selective non-small cell lung cancer [18, 19]. ICIs can block programmed cell death protein 1 (PD-1) by blocking programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), lymphocyte activation gene-3. The co-inhibitory signaling pathway mediated by immune checkpoints such as LAG-3 inhibits the killing of tumor killer cells on tumor cells and reactivates the immune response of human cells [20]. Other immune checkpoints such as T cell immune receptors with immunoglobulin and immunoreceptor tyrosine inhibitory motif domains, T cell immunoglobulin mucin region 3, immunostimulatory molecules B7H3 (also known as CD276), CD39, CD47, CD73, and other antibodies are under clinical study. ICIs have been extensively studied in gastric cancer, and some studies have shown remarkable efficacy. According to the application mode of clinical immune drugs, it can be divided into the following parts. **Figure 1** shows that perioperative immunotherapy for locally advanced gastric cancer.

ICIs monotherapy

In recent years, many studies have investigated the efficacy of ICI monotherapy in patients with untreated gastric or gastroesophageal junction cancer.

I. Pabolizumab monotherapy. In KEYMAT-062's Phase III trial [21], it was found that for patients with a combined positive score (CPS) of PD-L1 ≥1, the median overall survival in the Pabolizumab group was no worse than that of chemotherapy alone (cisplatin + fluorouracil; Capecitabine group (10.6 months vs. 11.1 months), but also did not show a significant advantage; For patients with PD-L1 CPS≥10, the median overall survival was 17.4 and 10.8 months, respectively, and the abolition monotherapy group showed numerical superiority: but, this difference was not statistically compared. The incidence of grade 3 to 5 adverse events was found to be 17% and 69% in the Pabolizon monotherapy group and chemotherapy alone group, respectively, suggesting that the Pabolizon monotherapy group was safer and better tolerated. In the KEYMAT-063 Phase III trial [22], it was found that the incidence of grade 3 to 5 adverse reactions in PD-L1 positive (CPS≥1) advanced gastric or gastroesophageal junction adenocarcinoma patients was 11% and 64%, respectively, and Pabolizil was more reliable than paclitaxel in terms of safety. Pabolizil did not show any advantage over paclitaxel in terms of median overall survival and median progression-free survival [8.0 months vs. 8.0 months, hazard ratio (HR) and 95% confidence interval (CI) of 0.99 (0.63, 0.95); 2.0 months vs. 4.0 months, HR (95%CI) was 1.62 (1.04, 2.52)]. Other second-line treatments, such as pabolizon in KEYNOTE-061 Phase III trials [23], did not extend overall survival in patients with PD-L1-positive advanced gastric or gastroesophageal junction adenocarcinoma. The above trial results suggest that ICI monotherapy Pabolizon has limited efficacy in the treatment of PD-L1-positive advanced gastric or gastroesophageal junction carcinoma patients, and stratification of PD-L1-positive patients may be needed to explore the efficacy of immune monotherapy or further explore treatment options suitable for different patients.

II. Study on the treatment of gastric or gastroesophageal junction carcinoma with Averumab. In the JAVELIN Gastric 100 trial [24], avilumab was used as maintenance therapy for advanced gastric

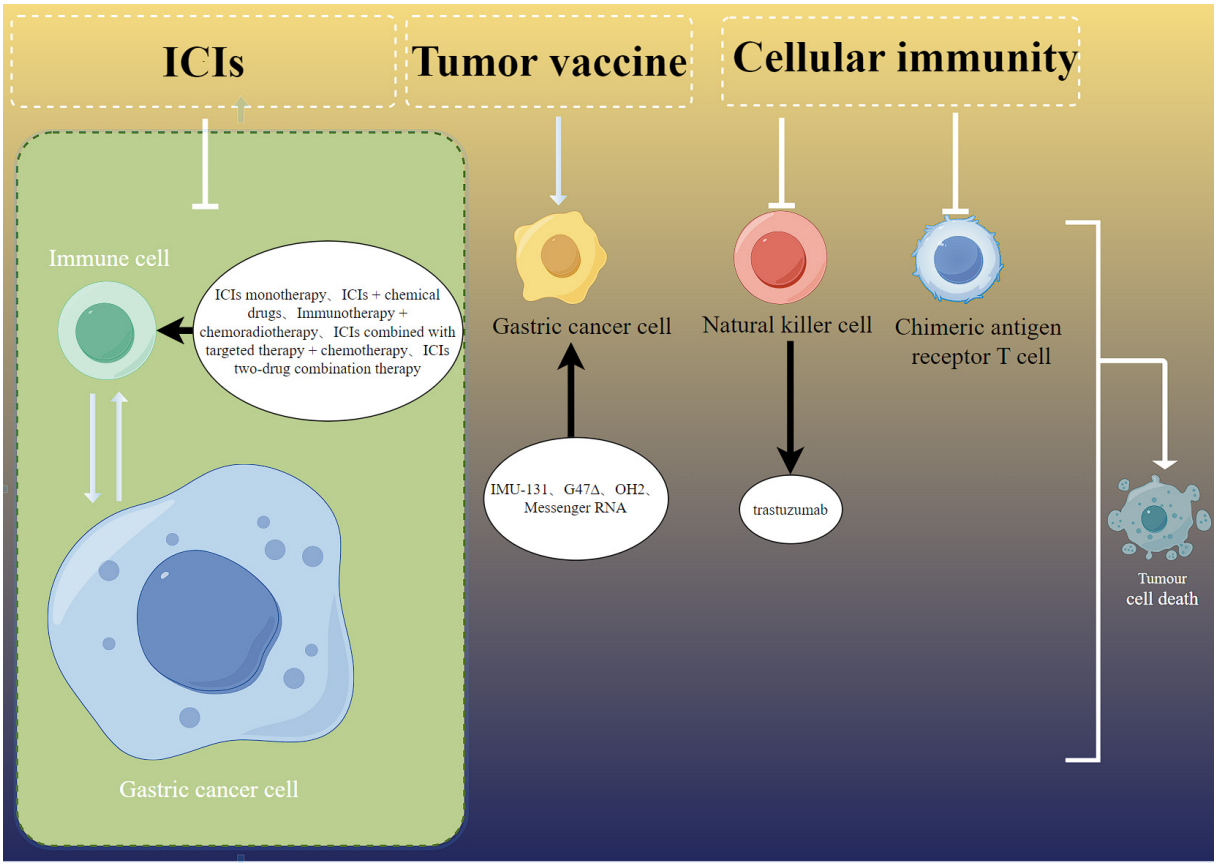

Figure 1. Perioperative immunotherapy for locally advanced gastric cancer. ICIs can block programmed cell death protein 1 (PD-1) by blocking programmed death-ligand 1 (PD-L1); The co-inhibitory signaling pathway mediated by immune checkpoints such as LAG-3 inhibits the killing of tumor killer cells on tumor cells and reactivates the immune response of human cells. ICIs: immune checkpoint inhibitors; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; CTLA-4: cytotoxic T-lymphocyte associated antigen 4; OH2: a genetically engineered oncolytic herpes simplex virus type 2; G47Δ: a kind of oncolytic virus.

cancer or gastroesophageal junction adenocarcinoma patients, and compared with chemotherapy alone, there was no advantage in median overall survival in the avilumab group (10.4 months versus 10.9 months). In PD-L1 positive (CPS≥1) patients, the median overall survival was 14.9 and 11.6 months, respectively (P=0.635), and averumab did not show better clinical outcomes, suggesting that when treating advanced gastric cancer or gastroesophageal junction adenocarcinoma, Avilumab maintenance therapy did not increase clinical benefit in all patients or PD-L1-positive patients, and its efficacy as a monotherapy in patients with advanced gastric cancer needs to be validated in further trials. Other PD-1 inhibitors [25], such as triplizumab in the treatment of advanced gastric cancer, found that the results of treatment with triplizumab monotherapy and its combination with XELOX (capecitabine and oxaliplatin) in patients with refractory gastric cancer showed that the objective response rates of the 2 groups were 12.1% and 66.7%, respectively. The disease control rate was 39.7% and 88.9%, the incidence of treatment-related adverse reactions was 77.6% and 94.4%, and the incidence of ≥ grade 3 treatment-related adverse reactions was 22.4% and 38.9%, respectively. PD-1 monoclonal antibody Tripril has a controllable safety profile and promising antitumor activity in the treatment of advanced gastric cancer and is more effective when combined with XELOX. In the above clinical trials, only KEYNOTE-062 showed a numerical advantage over chemotherapy in terms of median overall survival when Pabolizumab was used in the treatment of PD-L1 CPS≥10 patients, while the other trials showed efficacy equal to or no worse than chemotherapy in the treatment of PD-L1 positive patients. Although ICIs alone have no significant advantage over chemotherapy alone in terms of efficacy, they show good anti-tumor activity in combination with chemotherapy. The advantage of ICI monotherapy is that the efficacy of ICIs is not inferior to that of chemotherapy while the incidence of adverse reactions is low. Further studies can be conducted in the future to screen out ICIS monotherapy patients with greater benefits in terms of economy and efficacy.

ICIs combined with chemical drugs

The efficacy of ICI monotherapy in the treatment of advanced gastric cancer is not superior to chemotherapy, but a large number of studies have shown that ICI combined chemotherapy has better clinical outcomes than chemotherapy alone.

I. Parbolizol in combination with chemotherapy In the KEYKEYNOTE 059 trial [26], gastric cancer patients with PD-1 CPS≥1 were divided into Pbolizumab combined chemotherapy (combination group) and pbolizumab monotherapy (pbolizumab monotherapy group), and the results showed that the objective response rate of the combination group and Pbolizumab monotherapy group was 60.0% [95%CI (38.7%), 78.9%)] and 25.8% [95%CI (11.9%, 44.6%)], the combination showed better efficacy than the monotherapy, but parbolizul monotherapy

showed a lower incidence of grade 3 to 5 adverse events in terms of safety (76.0% vs. 22.6% in the 2 groups, respectively).

II. Nebuliumab in combination with chemotherapy In the ATTRACTION 4 trial [27], the difference in efficacy between the nabriliumab combined chemotherapy group (nabriliu group) and the placebo combined chemotherapy group (placebo group) was investigated, and the Nabriliu group did not show a significant advantage in terms of median overall survival (17.45 months vs. 17.15 months, P=0.26). However, it showed a significant benefit in median progression-free survival (10.45 months vs. 8.34 months, P<0.001), with a higher response rate and longer duration of response; also, in the CheckMate-649 Phase III trial [28], it was found that naboliuzumab combined with chemotherapy showed longer progression-free survival, longer duration of response, and a higher response rate in all randomized patients compared to chemotherapy alone. The results of the above two clinical trials all showed that nebuliumab combined with chemotherapy as first-line treatment had positive effects on human epidermal growth factor receptor type 2, Patients with HER2 negative, unresectable advanced or recurrent gastric cancer or gastroesophageal junction cancer may benefit.

III. Tirellizumab in combination with chemotherapy. In a Phase II NCT03469557 trial [29], the objective response rate and disease control rate of tirellizumab combined with chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma and gastric or gastroesophageal junction adenocarcinoma were 46.7% and 80%, respectively. The most common adverse event was anemia. This trial demonstrated that tirellizumab combined with chemotherapy has good efficacy and a manageable safety profile in advanced esophageal squamous cell carcinoma and gastric or gastroesophageal junction adenocarcinoma.

IV. Sindilizumab in combination with chemotherapy. Wu et al. [30] retrospectively analyzed the efficacy and safety of PD-1 inhibitor Xindilizumab combined with XELOX in patients with advanced gastric cancer, and the results showed that 1 out of 10 patients achieved clinical complete remission, 6 patients achieved clinical partial remission, and 3 patients had clinically stable disease without disease progression. None of the 10 patients had grade 3 or higher adverse reactions in terms of safety. The results suggested that the PD-1 inhibitor Sindilizumab combined with the XELOX regimen was effective for advanced gastric cancer. However, this study also pointed out deficiencies, that is, a small number of patients were included. In general, the results of most existing studies using immunotherapy combined with chemotherapy are encouraging. Immunotherapy combined with chemotherapy is better than chemotherapy alone in the treatment of advanced gastric cancer patients with PD-L1 CPS≥1, and the treatment of immunotherapy combined with chemotherapy can significantly improve the survival of patients. Only in the Phase III KEYNOTE-062 trial [21], it was found that pabolizumab combined with chemotherapy as the first-line treatment for patients with advanced gastric cancer with PD-L1 CPS≥1 or higher did not show better overall survival or progression-free survival than chemotherapy alone. This difference is worthy of further exploration for its reasons.

Immunotherapy combined with chemoradiotherapy

Radiotherapy can increase the efficacy of immune drugs. After radiotherapy, the expression of the major histocompatibility complex (MHC) on the tumor surface is upregulated, which enhances the recognition of tumor cells by cytotoxic T cells. At the same time, radiotherapy promotes the release of various cytokines, induces the activation of immune cells, changes the immune characteristics of tumors, and enhances the sensitivity of ICIs [31, 32]. In the perioperative treatment of locally advanced gastric cancer, a Phase II trial (NCT02730546) investigated the safety and efficacy of preoperative use of pabolizumab in combination with concurrent chemoradiotherapy in patients with gastroesophageal junction cancer. Seven patients (22.6%) achieved PCR but did not meet the prespecified primary endpoint [33]. However, in the II NeoPLANET(NCT03631615) trial, the application of neoadjuvant carrellizumab combined with chemoradiotherapy in locally advanced adenocarcinoma at the gastric or gastroesophageal junction was studied. The primary endpoint was the pathologic complete response (PCR rate was 33.3%(95%CI 18.6-51.0), which reached the pre-specified endpoint. The resection rates of TpCR, MPR, and R0 were 33.3%, 44.4%, and 91.7%, respectively. 77 patients (8.0%) achieved ypN0. The 2-year progression-free survival and OS rates were 66.9% and 76.1%, respectively [34]. Neoadjuvant carrilizumab combined with chemoradiotherapy has demonstrated a promising pathological response in patients with locally advanced gastric adenocarcinoma. In addition, in a multicenter, single-arm Phase II trial (ChiCTR1900024428), patients with locally advanced gastric cancer/gastroesophageal junctional adenocarcinoma received preoperative immunotherapy combined with chemoradiotherapy (anti-PD-1, S-1, and NAB-paclitaxel), followed by 3 cycles of adjuvant sindiglimab and chemotherapy. The primary endpoint was pCR. median disease-free survival (mDFS) and EFS were 17.0 (95%CI: 11.1-20.9) months and 21.1 (95%CI: 11.1-20.9) months, respectively. In 14.7 to 26.1 months, the median OS was not reached, and the 1-year OS rate was 92.6%(95%CI: 50.1 to 99.5) [35]. It is suggested that Sindilizumab combined with concurrent chemoradiotherapy has a promising effect in the perioperative treatment of locally advanced gastric cancer/gastroesophageal junction adenocarcinoma. Based on the results of the CROSS study, chemoradiotherapy has become the standard neoadjuvant therapy for patients with resectable esophageal cancer or gastroesophageal junction adenocarcinoma [36]. The PERFECT(NCT03087864) trial demonstrated the efficacy and safety of immunization combined with concurrent chemoradiotherapy in esophageal adenocarcinoma [37], but did not achieve the expected effect in the perioperative trial NCT02730546 in gastric cancer. Neo-PLANET and ChiCTR1900024428 studies demonstrated the effectiveness of immunotherapy combined with concurrent chemoradiotherapy in the perioperative treatment of advanced gastric cancer. Neoadjuvant PD-1 inhibitor combined with concurrent chemoradiotherapy may delay the progression of gastric cancer/gastroesophageal conjunctional adenocarcinoma. However, these two trials were single-arm designs with small sample sizes, and it is necessary to conduct a large-scale randomized controlled trial to further verify the efficacy of PD-1 combined with concurrent chemoradiotherapy in the perioperative treatment of locally advanced gastric adenocarcinoma. The application of immunization combined with concurrent chemoradiotherapy in perioperative gastric cancer is still under investigation.

ICIs combined with targeted therapy + chemotherapy

Targeted drugs themselves can inhibit the growth of tumor cells and, at the same time up-regulate the expression of PD-1 and its ligand, induce the expression of tumor-infiltrating lymphocytes, and up-regulate MHC II molecules [38-41]. At this time, the application of PD-L1 inhibitors can enhance the killing effect of immune cells. In several phase I/II studies, antiangiogenic agents have been shown to reprogram TME to reverse immunosuppression to an inflammatory state, working synergically with ICIs to promote a local immune response [42-44]. A single-arm Phase II exploratory trial (NCT03878472) evaluated the efficacy of neoadjuvant/translational therapy in combination with ICIs (carralizumab), anti-angiogenic agents (Apatinib), and

chemotherapy (S-1 ± oxaliplatin) in the treatment of cT4a/bN+ gastric cancer, the primary endpoint being pathological response and its potential biomarkers. PCR and MPR were 15.8% and 26.3%, respectively. Pathological reactions were significantly correlated with microsatellite instability, PD-L1 expression, and tumor mutation load [45]. However, it is important to note that the relatively short duration of treatment received by the patients in this study, including the number of treatment cycles and the interval between the last apatinib and surgery, may not be sufficient to achieve a fully materialized immune response, especially for patients with cT4 stage gastric cancer, and extending the duration of treatment may improve outcomes. In addition, the Dragon-Ⅳ / AAHEAD G208 study showed that the postoperative pCR rate of patients with advanced gastric cancer undergoing surgery after neoadjuvant therapy with Apatinib + carrilizumab +SOX regimen was 18.3%, which was significantly higher than 5.0% in the SOX regimen chemotherapy group [46]. This result confirmed the feasibility of the combination therapy mechanism of targeting, immunization, and chemotherapy, enriched the perioperative treatment options for patients with gastric cancer and brought hope for their long-term survival benefits. On the other hand, human epidermal growth factor receptor 2 (HER2) positive gastric cancer can be resected with perioperative chemotherapy combined with Tirelli.

The results of the study on therapeutic efficacy and safety of zumab and trastuzumab (NCT04819971) were presented at the ASCO meeting in 2023, and the pCR rate reached more than 58%, indicating the synergistic effect of the combination of anti-HER2 therapy and immunotherapy. The combination of anti-HER2 therapy and immunotherapy represented by Tirellizumab improved the efficacy of patients with HER2-positive gastric cancer. The TAOS-3B study (NCT05223088) explores the efficacy and safety of tirellizumab + Apatinib +SOX in the perioperative treatment of locally advanced gastric cancer, with promising results. Although the single-arm design of the combination therapy could not distinguish the relative contribution of each component (immunotherapy, targeted therapy, and chemotherapy) to the therapeutic effect and immune activation, in general, the combination of immune targeted therapy and chemotherapy achieved good efficacy in the perioperative treatment of locally advanced gastric cancer and enriched the treatment options for perioperative treatment of locally advanced gastric cancer. In patients with HER2-positive gastric cancer, the combination of anti-HER2 therapy and immune drugs will also create a new treatment model.

ICI two-drug combination therapy

The combination of anti-PD-1 antibody and anti-CTLA-4 antibody is theoretically different, and its complementary mechanism of action and specific efficacy are also different in different trials, showing promising anti-tumor activity in soft tissue sarcoma and osteosarcoma [47]. However, combined treatment with tisibumab based on platinum-etoposide and duvaliumab did not significantly improve the clinical outcome of patients with advanced small-cell lung cancer [48], suggesting that the efficacy of ICIs dual-drug combination should be further studied. In gastric cancer, the efficacy of ICIs in combination therapy has also been studied. In the study of Shitara et al. [49], it was found that for PD-L1 CPS≥5 and all randomized patients, the progression-free survival rate and objective response rate of the naboliumab combined with the ipilimumab group were not significantly improved compared with the chemotherapy group. However, the median duration of response was longer in the naboliumab plus ipilimumab group than in the chemotherapy group in PD-L1 CPS≥5 and in all randomized patients (13.2 months versus 6.9 months and 13.8 months versus 6.8 months). In the study of Kelly et al. [50], although the treatment of duvaliumab combined with tisibumab showed higher efficacy numerically than that of duvaliumab monotherapy, the overall remission rate and 6-month progression-free survival rate were still low, and ICIs combined with two drugs showed no significant clinical benefit. Moreover, due to the small sample size of the trial subgroup, the conclusion needed to be further verified. Although the complementary mechanism of action of anti-PD-1 antibodies and anti-CTLA-4 antibodies may theoretically lead to better clinical outcomes, no significant clinical benefit has been seen in existing trials. More related trials, such as PRODIGE 59-DURIGAST [51], are under investigation, but the results are not yet available.

Tumor vaccine

Tumor vaccine is another emerging field of tumor immunotherapy, mainly including polypeptide vaccine, dendritic cell vaccine, virus vaccine, messenger RNA vaccine, and so on. Most vaccines work by boosting the activation of a specific stage of immunity. A Phase I b study of IMU-131 (a HER2-targeting polypeptide vaccine) in patients with advanced HER2-overexpressed gastric cancer showed tumor shrinkage and tumor vaccine-specific immune responses in 11 of 14 patients, including 1 clinical complete response and 5 clinical partial response [52]. The clinical disease of 4 cases was stable and there were no vaccine-related serious adverse reactions, suggesting that the vaccine is safe and reliable in the course of treatment. At present, the Phase II trial of IMU-131 is underway, and the results are worthy of expectation. Dendritic cell vaccine has shown good antitumor activity in "cold" epithelial ovarian cancer [53], but the efficacy of dendritic cell vaccine in gastric cancer has not reached the expectation. Zhang et al. 's [54] study showed that when the dendritic cell vaccine prepared based on Wilm tumor protein-1 was used in the treatment of 3 patients with advanced gastric cancer, only 1 patient achieved clinical disease stabilization and the other 2 patients had disease progression. The dendritic cell vaccine for gastric cancer needs further exploratory trials. Oncolytic virus vaccines dissolve tumor cells, causing a cascade of tumor destruction as they multiply. Oncolytic virus G47Δ has shown good efficacy in residual or recurrent glioblastoma [55], and its good efficacy makes it the first approved oncolytic virus product in Japan. In solid tumors, Zhang et al. [56] showed that intra-tumoral injection of OH2 (a genetically engineered oncolytic herpes simplex virus type 2) has durable antitumor activity in patients with metastatic esophageal and rectal cancer, but relevant data in gastric cancer are not available, and further trials are needed to clarify the efficacy of oncolytic virus vaccine in patients with gastric cancer. The principle of messenger RNA vaccine is to screen out the best tumor antigen after gene sequencing of tumor tissue, synthesize the corresponding messenger RNA sequence in vitro, and then synthesize the target antigen after introduction in vivo to enhance the presentation of tumor antigen. A recent study of messenger RNA vaccine in pancreatic ductal adenocarcinoma showed that the median relapse-free survival of patients using the vaccine was longer than that of patients not using the vaccine [57]. In an ongoing trial of advanced metastatic solid tumors, a personalized xenochimp virus and a self-amplified messenger RNa-based neoantigen vaccine in combination with nabuliumab and ipilimumab have been shown to have a good safety profile, induce a durable neoantigen-specific CD8+T cell response, and prolong overall survival in several patients with microsatellite stabilized rectal cancer. Messenger RNA vaccines have shown promising anti-tumor activity and great anti-tumor potential, but there are currently no trials of messenger RNA vaccines in patients with gastric cancer.

Cellular immunity

Chimeric antigen receptor T cells and natural killer cells are common in cellular immunotherapy. Chimeric antigen receptor T cells have shown good efficacy in the treatment of hematological malignancies with high toxicity [58, 59]. Interim analysis of an open-label, single-arm, Phase I gastric cancer cell immunotherapy study in NCT03874897 showed that When 37 patients with advanced gastrointestinal cancer were treated with 2.5×108, 3.75×108, or 5.0×108 CT041 cells (genetically engineered autologous T cells expressing chimeric antigen receptors targeting CLDN18.2) [60], all patients experienced grade 3 or higher hematological toxicity. 94.6% of the patients had grade 1 ~ 2 cytokine release syndrome, and no ≥ grade 3 cytokine release syndrome or neurological toxicity occurred. The objective response rate and disease control rate were 48.6% and 73.0%, respectively, and the 6-month disease control rate was 44.8%. The objective response rate, disease control rate, and 6-month overall survival rate of gastric cancer patients were 57.1%, 75%, and 81.2%, respectively, suggesting that chimeric antigen receptor T cell therapy showed good efficacy in gastric cancer, and showed a trend of better efficacy in patients with higher expression of CLDN18.2 site. However, the results of this experiment are preliminary observations and need to be verified by further studies. Natural killer cell immunotherapy is safe and effective in neuroblastoma [61]. Results in HER2-positive solid tumor patients show that natural killer cell immunotherapy combined with trastuzumab shows some efficacy and safety [62], but further trials are needed to confirm the specific efficacy of natural killer cell immunotherapy in gastric cancer.

Summary and prospect

With the deepening of immunotherapy research, gastric cancer immunotherapy strategies are also improving. ICI monotherapy has not shown particularly good performance as a first - or second-line treatment, but it has shown good clinical efficacy in combination with other approaches such as chemical and targeted agents in most trials, especially in combination with anti-HER2 antibodies. Cellular immunotherapy and tumor vaccines have great potential for treatment and have shown good efficacy in some tumors. They are the direction of precision tumor medicine in the future and also the hot spot of future research. We are looking forward to breakthroughs in the field of immunotherapy for advanced gastric cancer. In addition, there is a lack of appropriate, standardized biomarkers to select patients most likely to respond to immunotherapy, and identifying these biomarkers is critical given the high proportion of patients who do not respond and the increased risk of toxicity and cost associated with the use of immunotherapy. It is expected that immunotherapy can be explored more deeply in the future so that patients with locally advanced gastric cancer with oligometastasis or small tumor load can use immunotherapy for neoadjuvant/conversion therapy so that they can receive radical surgical treatment, improve the R0 resection rate, and ultimately improve the survival benefit of patients.

Acknowledgements

None.

Availability of data and materials

Data and materials are available on request from the authors.

Ethical policy

Not applicable.

Author contributions

SBM and WZ conceptualized, designed, conducted research, and wrote the first draft. XDG, AND YHC contributed to the revision and figure production, ZYZ amd JBJ provided supervision and revision of the draft.

Competing interests

The authors have no conflicts of interest regarding the publication of this paper.

Funding

None.

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