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New Era of Immune Checkpoints in Advanced Gastric Cancer

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Abstract

Gastric Cancer (GC) is a common cancer worldwide, and immunotherapy as a new breakthrough has become one of the important anti-tumor treatment modes. Immune Checkpoint Inhibitors (ICI) mainly activates the immune system by blocking PD-1/PD-L1 and CTLA-4, which is one of the main therapeutic approaches in immunotherapy. Currently, clinical trials of immune checkpoint inhibitors have been successfully used as adjunctive therapy for resectable and unresectable in AGC. At the same time, the analysis found that the data of immune checkpoint inhibitors in the Asian population showed a statistically significant overall survival advantage over the Western population. Therefore, this review reviews the recent progress of immunocheckpoint inhibitors in neoadjuvant/adjuvant therapy for AGC and in the late treatment of unresectable GC, and describes the significant characteristics and broad application prospects of ICI in Asian population.

Keywords: Advanced gastric cancer; Adjuvant therapy; ICI; CLDN18.2

Introduction

The global cancer data for 2020 shows that 49.3% of all cancers in the world are in Asia, with China accounting for about a quarter of the total. The cancer death rate in Asia was 58.3% [1]. The study using open-source data in 2022 showed that the incidence and mortality of cancer in China were far higher than that in the United States. Although GC showed a declining trend in global data, it still occupied the top three in China, accounting for more than 50% of global cases [1-3]. Radical gastrectomy is recognized as the best treatment for gastric cancer [4]. However, some patients with resectable advanced gastric cancer need combined neoadjuvant therapy to improve postoperative tumor-free survival and overall survival, while other unresectable patients can only consider late anti-tumor therapy to prolong survival time. The efficacy of traditional chemotherapy is limited, and the mOS (median Overall Survival) are only about 8 months [5]. Therefore, the treatment mode of GC has gradually changed in recent years, and immunotherapy has become a new anti-tumor treatment mode in perioperative adjuvant therapy and late treatment of recurrence and metastasis [6,7]. Some studies have also shown that the targeted combined immunotherapy for HER-2 positive gastric cancer patients has achieved good results [8]. Therefore, this paper reviews the latest research progress of immune checkpoint inhibitors in gastric cancer and the data analysis of Asian populations in the past clinical trials of immunotherapy for gastric cancer, in order to provide further data support for the progress of immune checkpoint inhibitors in China.

Anti-PD-1/L1

Neoadjuvant/Adjuvant therapy for resectable advanced gastric cancer

D2 radical surgery and adjuvant chemotherapy is mainly treatment scheme of Gastric/Gastroesophageal Junction (G/GEJ) cancer [9]. The resolve study showed that perioperative treatment had significant clinical improvement on D2 gastrectomy in locally advanced gastric cancer/GEJC patients [10]. In recent years, a phase II study of perioperative immunotherapy for gastric cancer has been carried out in China (ChiCTR2100043572), with the main purpose of evaluating the 2-year DFS rate after perioperative treatment of PD-1 combined with oxaliplatin/gio (SOX regimen) for locally resectable advanced gastric adenocarcinoma. A total of 21 patients were included, and the R0 resection rate was 100%. Results Postoperative pathology showed 7 patients (33.3%) achieved pathological Complete Response (pCR), 8 patients (38.1%) had major response (TRG 0-1) and 21 patients (100%) achieved R0 resection [11]. A phase II trials of PD-1 inhibitor Tislelizumab combined with S-1 plus Oxaliplatin (SOX) in Patients with Local Advanced G/GEJ cancer (NCT04890392). Results showed 13 of 21 patients (61.9%) reached tumor Major Pathology Response (MPR) after treatment and 5 of 21 patients had a complete tumor response (23.8%) [9].

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Recently, based on the CheckMate 577 study [12], the US Food and Drug Administration included Natalizumab in the treatment of locally advanced EGC in the 2021 ASCO update, and further study confirmation in the AGC is expected in the future. A meta-analysis of 13 Phase I/II clinical trials including 332 patients with resectable gastric cancer treated with neoadjuvant ICI had pCR, MPR, and R0 removal rates of 16%, 36%, and 97% [13]. In conclusion, neoadjuvant/adjuvant immunotherapy in locally advanced gastric cancer is a new direction in the future, which is expected to improve the prognosis and prolong the survival time of patients.

Clinical trials of unresectable advanced gastric cancer

Recently, Zhang et al. [14] through meta-analysis showed that immunotherapy in Asia (HR: 0.80; 95% CI: 0.65-0.98) *vs.* western (HR: 0.90; 95% CI: 0.81-1.00) patients had different Overall Survival (OS), and Asian patients had a significant advantage in OS compared with western patients (P=0.04). Therefore, AGC as a geographically heterogeneous disease, it is necessary to further explore the treatment of gastric cancer in Asia through key clinical trials, especially in third-line and first-line treatments, which have achieved good results.

Third or later-line setting

In 2014, The ATTRACTION-2 third-line immunotherapy is the first randomized, double-blind, placebo-controlled Phase III clinical trial based in Asia. A total of 493 patients with AGC or Gastroesophageal Junction Carcinoma Cancer (GEJC) with at least past chemotherapy failure or intolerance were enrolled in Japan, Korea, and Taiwan, China. Compared with placebo, nivolumab patients had longer mOS (5.26 *vs.* 4.14 months) and significantly higher OS rates (27.3%, 10.6%, and 5.6%) at 1, 2, and 3 years of follow-up (11.6%, 3.2%, and 1.9%). The mOS of 3 years reached 26.68 months. In terms of safety, nivolumab had a manageable grade 3 to 4 adverse reaction rate of 10%. Therefore, nivolumab is the first immunotherapy approved for gastric cancer in the world, especially in Asian patients, confirming the efficacy and safety of immunotherapy in Asian patients [15-17]. The Keynote-012 study, which included a small number of Asian populations in Korea and Taiwan, showed similar survival in Asian and non-Asian patients treated with pembrolizumab monotherapy [18]. Subsequently, kenote-059 further evaluated the safety and efficacy of pembrolizumab as a third-line treatment. In the whole population, ORR was 11.6% (95% CI: 8.0%-16.1%), in which THE ORR ratios of PD-L1 positive (CPS ≥ 1) and PD-L1 negative (CPS<1) were 15.5% and 6.4%, respectively [19]. Based on kenote-059 and Attract-2 studies, pembrolizumab and nivolumab were approved by the US Food and Drug Administration (FDA) and the National Medical Products Administration (NMPA) in September 2017 as indications for third-line and subsequent treatment of GC [20,21].

Second-line therapy

Keynote-061 is an early global Phase iii study comparing Paclitaxel with Pablizumab as a second-line treatment for gastric cancer. The results showed that second-line treatment with pD-L1 positive gastric cancer patients with PD-L1 significantly prolonged OS, and the drug had better safety [22]. Data published in 2021 from keynote-063 showed no significant increase in survival or therapeutic efficacy with pabolizumab, but a manageable safety profile. The mOS, mPFS, 13% ORR, and median Duration of Remission (DoR) were 8 months in the pembrolizumab group. The paclitaxel group was 8 months (HR: 0.99, 95% CI 0.63-1.54), median PFS was 4 months (HR: 1.62, 95% CI 1.04-2.52), ORR was 19%, and DoR was 12 months. In terms of safety, the incidence of treatment-related Adverse Events (AE) was 60% in the pabolizumab group and 96% in the paclitaxel group [23]. In this study, pD-1 mab was found to be safer than paclitaxel in second-line treatment of PD-L1 positive GC, but no benefit was shown.

Further clinical trials are still needed to explore the possibility of immunotherapy in second-line treatment of advanced gastric cancer patients in Asia.

First-line setting

Results from four key Phase III trials in first-line therapy for AGC demonstrated efficacy and safety of anti-PD-1/PD-L1 inhibitors in the Asian population. We found in keynote-062 was that the data in the Asian population was significant. A total of 763 patients were enrolled, including 187 in the Asian population who were randomly assigned equally. Results Pembrolizumab outperformed chemotherapy in both PD-L1 CPS ≥ 1 and CPS ≥ 10 subgroups in the Asian population, with a significant benefit (HR: CPS ≥ 1, 0.54; CPS ≥ 10, 0.43). The 12-month OS rate in the pembrolizumab monotherapy group (CPS ≥ 1, 69% *vs.* 54%; CPS ≥ 10, 81% *vs.* 68%) and 24-month OS rate (CPS ≥ 1, 45% *vs.* 23%; CPS ≥ 10, 54% *vs.* 27%), and the difference in OS rate at 24 months was more than 20% [24]. Thus, pembrolizumab benefited regardless of CPS expression on OS in the Asian subgroup, with higher CPS expression indicating better efficacy. The Attraction-4 is a trial evaluating the efficacy and safety of nivolumab as a first-line treatment primarily in Asia (Japan, South Korea and Taiwan). Nivolumab combined with chemotherapy significantly improved progression-free Survival (PFS, HR: 0.68; 98.51% CI, 0.51 to 0.90; P=0.0007; mPFS, 10.5 *vs.* 8.3 months). The ORR of nivolumab combined with chemotherapy was higher than that of chemotherapy (57.5% *vs.* 47.8%; P=0.0088). Nivolumab combined with chemotherapy showed significant improvement in PFS and clinically significant improvement in PFS and ORR. The clinical data from the Asia-wide population showed the potential of nivolumab as a new first-line treatment option for patients with advanced or relapsed G/GEJ cancer [25]. The CheckMate 649 study in 2020 [26] was conducted simultaneously at more than 20 centers in mainland China, and a total of 208 Chinese patients were enrolled. Extended data from the CheckMate 649 Study in China were published in April 2021 showing that patients in China were more likely to benefit from a first-line regimen of nivolumab in combination with chemotherapy. In the Chinese subgroup, pD-L1 CPS ≥ 5 accounted for 75% of all randomized Chinese patients. Nivolumab combined with chemotherapy extended the mOS from 9.6 to 15.5 months in Chinese patients with PD-L1 CPS ≥ 5 (HR: 0.54 [95% CI 0.36-0.79]). mPFS extended from 4.3 to 8.5 months (HR: 0.52 [95% CI 0.34-0.77]). Among the Chinese patients with PD-L1 CPS ≥ 5, ORR in the nivolumab combined chemotherapy group reached 68%, which was much higher than that in the chemotherapy group alone (20%). Compared with the global population, the Chinese subgroup showed more significant improvement in OS, PFS and ORR. The successful combination of nivolumab with chemotherapy based on CheckMate 649 has become the standard first-line treatment for non-HER-2 positive advanced GC.

Orient-16 [27] is a phase III study evaluating first-line localized AGC with Sintilimab in all Chinese patients. Mid-term results in 2021 showed that a total of 650 patients included 397 (61.1%) with CPS ≥ 5 and patients with CPS ≥ 5 were treated with Sintilimab vs. chemotherapy (mOS: 18.4 vs. 12.9 months; P=0.0023) and overall patients had significantly longer OS (mOS: 15.2 *vs.* 12.3 months; P=0.0090). Patients with CPS ≥ 5 (mPFS 7.7 *vs.* 5.8 months,

P=0.0002) and all patients (mPFS 7.1 *vs.* 5.7 months, P<0.0001) in the Sintilimab group were better than those in the chemotherapy group in terms of PFS. The ORR of patients with CPS ≥ 5 and sindilizumab combined with chemotherapy was significantly higher than that of the control group (72.8% *vs.* 59.6%, respectively), and the mDOR was 8.4 *vs.* 5.5 months, respectively. In terms of adverse reactions, there were 196 grade 3 Treatment-Related Adverse Events (TRAE) and 6 deaths in the Sindili combined chemotherapy group, while there were 168 Grade 3 TRAE and 2 deaths in the chemotherapy group, indicating an acceptable safety. The results show a dual victory in both PFS and OS. A 2022 study by Dubois et al. [28] through a meta-analysis suggested that ICI and standard first-line chemotherapy tend to be used in combination regardless of PD-L1 CPS status, which is expected to prolong the survival time and improve the prognosis of patients with AGC.

Anti-CTLA-4

Anti CTLA-4 inhibitor and combined immunotherapy

In 2011, FDA first approved anti-CTLA-4 inhibitor ipimab to treat patients with advanced melanoma, successfully opening a new field of anti-CTLA-4 inhibitor tumor treatment [29,30].

Ipilimumab is the only CTLA-4 inhibitor approved for advanced melanoma patients in the United States in 2011. Currently, it has not been approved in GC, and relevant clinical trials have recently obtained partial data [31]. In 2018, Yanfang et al. [32] in Beijing reported a patient with locally advanced GC who was admitted to hospital in June 2010 and received 8 times of Ipilimumab combined with lapatinib in the second line. At long-term follow-up, the patient survived for more than 4 years after multiple lymph node metastases. This case study suggests that targeted therapy combined with immunotherapy may be an effective option for the treatment of advanced gastric cancer. In 2016 [33] Ipilimumab was used to treat advanced GC/GEJ adenocarcinoma in a Phase II clinical study (NCT01585987). The Ipilimumab group and chemotherapy group had an OS of 12.7 and 12.1 months, respectively, which did not meet the expected end point. The relevant trials of Ipilimumab are still in the process of further exploring the reasons for failure. At present, the efficacy of Ipilimumab combined with PD-1 inhibitor in the late stage is actively carried out at home and abroad. CheckMate-032 is a Phase I/II clinical trial evaluating the safety and efficacy of nivolumab and nivolumab plus ipilimumab in advanced GC in the West [34]. Results of the 2017 study showed that 79% of the 160 patients treated received two or more treatments. The objective response rates assessed by the researchers were 12 percent, 24 percent and 8 percent, which were statistically significant. Median follow-up was 28, 24, and 22 months, with progression-free survival at 12 months of 8%, 17%, and 10%, respectively. The OS rates at 12 months were 39%, 35% and 24%, respectively. Three quarters of treatment-related adverse events (17%, 47%, and 27%, respectively) were reported in each of the three groups. Results showed that nivolumab and nivolumab plus ipilimumab showed clinically significant antitumor activity and controllable safety in patients with chemotherapy-refractory GC, and nivolumab combined with ipilimumab is expected to achieve the status of third-line treatment for advanced GC [35]. Therefore, a subgroup of nivolumab plus Ipilimumab was established in the CheckMate 649 trial. Preliminary results in 2022 showed that the overall survival rate of PD-L1 CPS ≥ 5 did not meet the predetermined endpoint after 12 months of follow-up. Only continued use of nivolumab plus chemotherapy is supported as standard first-line treatment for advanced GC [36]. In conclusion, the efficacy of Ipilimumab in advanced gastric cancer needs further experimental confirmation, especially the CheckMate-032 study mainly targeted at the Western population, due to regional differences, whether ipilimumab single drug and double free treatment can achieve good efficacy in patients with advanced gastric cancer in China needs further verification and exploration. In 2021, Sejung et al. [37] included 7 randomized controlled trials involving 2,601 patients and 9 treatments. The results showed that nivolumab combined with ipilimumab (HR: 0.59, 95% CI: 0.38-0.91) was the most effective treatment and most likely to improve PFS. Nivolumab was even better at improving ORR. Nivolumab is also one of the best options for a benefit-risk ratio. Therefore, nivolumab combined with ipilimumab double free treatment to improve the survival of patients with advanced GC is worthy of further exploration.

CLDN18.2

Tight junction proteins (Claudins) were first identified and named by Mikio Furuse and Shoichiro Tsukita in 1998 [38]. Claudins, a small molecule (20~24/27 kda) quadronal transmembrane protein, is a member of Claudin (CLDN) protein family, which has two isomers Claudin18.1 and Claudin18.2. The expression of Claudin18.2 protein is tissue specific, and CLDN18.2 is only expressed in differentiated epithelial cells of gastric mucosa under normal physiological conditions. After malignant transformation, CLDN18.2 epitope was exposed. Claudin18.2 is usually overexpressed in solid tumors [39]. Claudin18.2 is usually buried in tissue cells, and the occurrence of malignant tumors will lead to the destruction of tight connections, exposing the Claudin18.2 epitope on the surface of tumor cells and becoming a specific target [40]. Therefore, Claudin18.2 may be an effective target in solid tumors such as GC [39]. In particular, Claudin18.2 has a positive rate of nearly 60% in all patients with GC, and has a lower HER2-positive mutation rate than patients with gastric cancer, which may have a broader benefit potential [41].

Zolbetuximab

Zolbetuximab is the first monoclonal antibody to target Claudin18.2 [42]. Data from the Phase II FAST trial of Zolbetuximab in combination with first-line chemotherapy in GC patients with advanced Claudin18.2 positive expression were published in 2016. The combined treatment with Zolbetuximab significantly increased mPFS (5.7 *vs.* 7.9 months) and mOS (8.7 *vs.* 12.5 months) compared with EOX alone. The latest data from the trial were published in Annals of Oncology this year showed that mPFS and mOS were 9 and 16.5 months, respectively, in patients with Claudin18.2 positive tumor cells >70% [43]. Martin et al. [44] conducted Claudin18.2 analysis on tumor tissue samples from patients in FAST test, and the results showed that nearly half of the FAST test was positive for Claudin18.2. These data suggest that Claudin18.2 may be used as a non-HER2 overlapping targeted change in different subgroups of gastric cancer patients, which is a meaningful new targeted immunotherapy in the future. In 2019, a phase II study of Zolbetuximab showed that patients receiving Zolbetuximab in combination with chemotherapy in advanced GC showed longer PFS and OS. Especially in patients with Claudin18.2 positive cells >70%, the mOS of Zolbetuximab combined with chemotherapy group was nearly doubled (16.5 *vs.* 8.9 months) [45]. In 2021, Sahin et al. [46] published a first-line Phase II clinical trial of Zolbetuximab combined with chemotherapy and chemotherapy group for advanced CLDN18.2 positive G/GEJC. In the general population, both PFS (HR=0.44; 95% CI, 0.29 to 0.67;

P<0.0005) and OS (HR=0.55; 95% CI, 0.39 to 0.77) significantly improved. PFS benefits were also shown in patients with moderate CLDN18.2 expression in ≥ 70% of tumor cells (HR=0.38; 95% CI, 0.23 to 0.62; P<0.0005). The majority of adverse events in the zolbetuximab group were grading 1-2 compared with those in the chemotherapy group. This study showed that Zolbetuximab combined with chemotherapy can prolong the survival of patients with advanced GC, and the higher the expression of CLDN18.2, the better the efficacy and the safety is controllable. Zolbetuximab as Claudin18.2 mAb is a promising new star in immunotherapy, and is expected to be used in the first-line treatment of adult patients with advanced GC who are Claudin18.2 positive and HER2 negative in the future.

Claudin18.2 CAR-T therapy

CAR-T immunotherapy is an important representative method of adoptive cell immunotherapy, which refers to the expression of receptors that can specifically recognize tumor cell antigens on the surface of T cells through genetic engineering technology [47]. In CAR T therapy, patient T cells are genetically engineered to express the Chimeric Antigen Receptor (CAR), which converts any specific T cells into tumor-specific T cells that can be expanded to large numbers and redistributed to patients to eliminate cancer cells, including metastases. This approach has received five FDA approvals to date in hematologic tumors, however only CT041 has achieved partial success in advanced GC. Here, we briefly discuss some promising attempts to apply this technique to gastrointestinal cancer [48].

CT041 is the first autologous CAR T cell therapy targeting Claudin18.2 in the world. CT041 received its first clinical approval in the United States in May 2020; in August, for the first time, advanced G/GEJC was approved for clinical treatment in China for indications of at least second-line treatment failure [5,49]. A Phase Ib/II clinical trial of CT041 in advanced G/GEJC subjects has been initiated. In October 2020, FDA granted orphan drug designation for the treatment of G/GEJC [50]. In 2021, the phase I trial of Claudin18.2-specific CAR T cells in gastrointestinal cancer conducted by Peking University Cancer Hospital in China announced the interim results. A total of 37 patients were enrolled in the trial, including 28 patients with gastric cancer. Patients were given CT041 in three dose groups, 2.5×108 (28 patients), 3.75×108 (6 patients), and 5×108 (3 patients). Interim results showed that ORR and DCR of 37 patients were 48.6% and 73.0%, mPFS was 3.7 months, and OS rate at 6 months was 80.1%, among which ORR and DCR of gastric cancer patients were 57.1% and 75.0%, respectively. In terms of safety, all patients experienced grade 3 hematological toxicity, and 94.6% patients developed grade 1 or 2 cytokine release syndrome, without other serious AE [51]. This study is the first to demonstrate that CT041 has good antitumor activity and acceptable safety in patients with refractory CLDN18.2+ gastrointestinal tumors.

Summary and Outlook

Immunotherapy, as an important means of cancer treatment, has made a breakthrough in advanced gastric cancer in recent years. It has great prospects and is also the focus and hotspot of current research. Data analysis of immune checkpoint inhibitors in Asia and even China shows that the efficacy is more significant than that in the West, but clDN18.2 targeted immunotherapy remains to be further verified. At present, good results have been achieved in the late treatment of unresectable gastric cancer, but the efficacy of neoadjuvant therapy needs to be further studied and discussed. Therefore, the publication of relevant clinical data in the future will be our focus, as well as the importance of further including more Chinese population to guide immunotherapy in advanced gastric cancer patients in China.

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