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PROSPECTS FOR THE TREATMENT OF METASTATIC GASTRIC CANCER

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Abstract:

The surgical method is the main method of treatment for almost all types of malignant neoplasms of the stomach.

For patients who cannot undergo radical resection or with metastatic disease, comprehensive treatment based on systemic antitumor therapy such as palliative surgery, radiation therapy, radiofrequency ablation (RF), intraperitoneal perfusion and arterial embolization is recommended, as they can help prolong survival and improve quality of life. Such cases should be discussed in an interdisciplinary commission for an optimal personalized treatment strategy.

Keywords: gastric adenocarcinoma, anti-angiogenic chemotherapy, laparoscopic gastrectomy; esophageal entero anastomosis.

Combined chemotherapy is recommended because it has been associated with a response rate of 30%-54% and a median S (mOS) of 8-13 months [1]. For those who cannot tolerate combined chemotherapy, you can consider chemotherapy with one drug, for example, monotherapy with 5-fluorouracil.

Radiation therapy can significantly alleviate some of the clinical symptoms of late-stage RV, such as hemorrhage, severe cancer pain, dysphagia and obstruction, and can improve the general condition and quality of life of patients [2, 3, 4].

Palliative radiation therapy may be considered for elderly patients with progressive disease, decreased cardiopulmonary functions, multiple underlying diseases and difficulties in maintaining surgical intervention.

Three-dimensional conformal radiation therapy (3D-CRT) and intensely modulated radiation therapy (IMRT) are recommended because relevant studies have shown that, compared to conventional two-dimensional radiation therapy, 3D-CRT or IMRT were excellent in targeting the dose distribution area and protecting normal organ tissue, especially in the gastrointestinal tract, liver and kidneys, from adverse events from radiation [5, 6].

Currently, the main drugs for the treatment of stomach cancer in China consist of chemotherapy, targeted therapy and immune checkpoint inhibitors. For chemotherapy, there is enough evidence-based evidence and experience in clinical practice to support their use.

As for targeted therapy, although extensive studies have been conducted on its use in RV, only a few targeted drugs have been approved for clinical practice, that is, anti-HER2 drugs such as trastuzumab and anti-angiogenic pathway drugs such as apatinib.

As for immunotherapy, despite the breakthroughs in research concerning antibodies to PD-1, immunotherapy with one drug was not satisfactorily effective.

Due to the heterogeneity of RV complicated by the tumor microenvironment, inconsistent epidemiological characteristics of patients with gastric cancer in the East and West, differences in clinical and pathological characteristics and a wide choice of medications, suitable patients should be encouraged to participate in appropriate clinical trials.

The general prognosis of progressive Russian Railways is unfavorable. Traditional chemotherapeutic drugs remain among the last available evidence-based therapies, as the choice of targeted drugs remains limited, and the effectiveness of immunotherapy alone is not satisfactory. Thus, given the heterogeneity of gastric cancer, these patients are invited to participate in clinical trials for the development of precision medicine.

Fluoropyrimidine, platinum and taxanes are the main therapeutic drugs for the treatment of late-stage RV. Usually, first-line regimens are based on fluoropyrimidine in combination with platinum and/or taxanes to make up a regimen with two or three drugs [1, 7, 8, 9, 10, 11, 12, 13, 14, 15].

In China, a two-drug therapy consisting of fluoropyrimidine and platinum is recommended, and oxaliplatin is preferable to platinum, based on Chinese real data and better observed tolerability [9, 13].

In the phase III clinical trial of SOX-GC [13], the efficacy of SOX and SP as first-line treatment for diffuse or mixed progressive gastric

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adenocarcinoma/EGJ was compared. The results showed that compared to the SP mode, the SOX mode was associated with a certain degree of improvement in efficiency, survival and tolerance. In addition, the incidence of grade ≥3 side effects, such as neutropenia, anemia, nausea, vomiting, nausea, vomiting, anorexia (with the exception of sensorineural toxicity), was significantly lower in the SOX group than in the SP group. Therefore, the SOX regimen is recommended as the first choice of treatment for non-intestinal stomach cancer.

Paclitaxel in combination with fluorouracil has shown sufficient efficacy and safety in clinical trials and in practice [10].

Although the three-drug DCF regimen has reached its endpoint in phase III clinical trials, its high toxicity limits its clinical use [11].

Modified docetaxel plus cisplatin plus 5-fluorouracil (mDCF) [12] and paclitaxel plus FOLFOX (POF) regimens [16] have been shown to be more effective and tolerable than the two drug regimens in randomized trials.

However, the phase III study showed that the addition of docetaxel to cisplatin and S-1 did not improve OV during chemotherapy - naive, inoperable or recurrent RV [17].

The phase II study showed that the efficacy and survival of docetaxel plus oxaliplatin plus 5-fluorouracil (TEF) are superior to the regimens of docetaxel plus oxaliplatin (TE) or docetaxel plus oxaliplatin plus capecitabine (TEX) [18].

The choice of chemotherapy regimen should be based on the patient's age, physical condition, concomitant diseases, previous treatment, patient readiness, economic status, possible bias in clinical practice and availability of medications.

There is insufficient evidence to recommend chemotherapeutic drugs based on the prediction of a chemotherapeutic response in accordance with the Loren classification, molecular classification, in vitro drug susceptibility test, xenograft transplantation model, xenobiotic metabolism or metabolomics.

Patients with suspected fluoropyrimidine-associated metabolic disorders are recommended to undergo a test for dihydropyrimidine dehydrogenase deficiency (DPD) [19], and those with suspected irinotecan-associated metabolic disorders can undergo testing for UGT1A1 gene polymorphism [20].

Standard treatment for late-stage stomach cancer usually lasts 4-6 months, and these patients should be regularly monitored after disease control. A randomized controlled phase III trial showed that first-line chemotherapy with paclitaxel plus capecitabine therapy followed by capecitabine for maintenance (PACX) was not associated with an improvement in median progression-free survival (mPFS) and mOS compared to the XP regimen, but significantly improved quality of life and reduced adverse events associated with treatment [10].

Studies have shown that two-drug regimens were better than single-drug regimens for elderly or debilitated patients [21, 22].

In the GO2 study [15], elderly or debilitated patients were randomly assigned the following three dose levels: A: oxaliplatin 130 mg/m2 + capecitabine 625 mg/m2 (twice a day for 1-21 days, every 3 weeks); B: 80% dosage of level A; C: 60% dosage of level A A. The results showed that compared to the level A and B dose, patients with a level C dose not only had no worse results in terms of PFS, but also had better overall treatment outcomes (overall therapeutic efficacy, toxicity and quality of life).

Currently, the results of second-line chemotherapy studies comparing the effectiveness of treatment with one drug have shown that for patients with the efficacy index of the Eastern Cooperative Cancer Group (ECOG PS) 0-1, chemotherapy with two drugs was safe and was associated with better tumor control, although the size of the study cohort was relatively small [23, 24].

Therefore, for patients with good physical condition, after fully weighing the pros and cons of treatment, combined chemotherapy can be considered.

The Japanese clinical trial CLASS02 phase III showed that weekly paclitaxel associated with albumin nanoparticles (nab-paclitaxel) is not inferior to weekly solvent-based paclitaxel in terms of S [25]. Neutropenia and loss of appetite were more common in the nab-paclitaxel group, but the frequency of hypersensitivity was lower.

Clinical studies concerning the treatment of late-stage third-line gastric cancer, although consisting of a limited number of patients, did not find significant benefit from chemotherapy in this group of patients. The risks and benefits of treatment should be carefully weighed depending on the physical condition of the patients, the underlying diseases, symptoms associated with the tumor, and the risk of complications.

The ToGA study [26] showed that, compared with monochemotherapy, trastuzumab in combination with first-line chemotherapy was associated with improved efficacy and survival in patients with HER2-overexpressed late RV. A number of phase II clinical trials evaluated the combination of trastuzumab and other chemotherapy regimens, demonstrating good efficacy and safety [27, 28].

The EVIDENCE study [29] was organized to evaluate the efficacy, safety, treatment regimen and

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clinical results of trastuzumab in Chinese HER2-positive patients with metastatic gastric cancer. His results showed that, compared with chemotherapy, trastuzumab was associated with an improvement in OV and PFS in Chinese patients with metastatic RV HER2+, was well tolerated and was effective in combination with a number of other treatment methods in real conditions.

In the case of combined chemotherapy using the XELOX regimen, the best efficacy of trastuzumab was demonstrated at 34.6 months [30].

For HER2-positive patients with late-stage gastric cancer without prior use of trastuzumab, paclitaxel in combination with trastuzumab was recognized as effective and safe in a Chinese phase II clinical trial [27].

However, after the failure with trastuzumab, recent data from phase II clinical trials and retrospective analyses have shown different significance for the use of trastuzumab cross-line, and more evidence is needed [27].

In 2020, the "Chinese Expert Consensus on Drug Analogues" approved the clinical replacement of drug analogues. In August 2020, the National Administration of Medical Devices (NMPA) of China approved the indications for the use of trastuzumab analog HLX02 for HER2-positive breast cancer and a combination of capecitabine/5-FU and cisplatin for newly diagnosed, metastatic, HER2-positive stomach cancer.

There is no positive response from other HER2-targeted drugs, including pertuzumab (anti-HER2 mAb, JACOB study) [31], lapatinib (small molecule tyrosine kinase inhibitor; LOGIC and TyTAN study) [32, 33], and antibody-drug conjugate (ADC) TDM-1 (drug-related anti-HER2 mAb) [34], as a second-line treatment for metastatic gastric cancer in phase II clinical trial was not observed. The use of ADCs targeting HER2 remains promising.

Ramucirumab (anti-VEGFR2 mAb) and apatinib mesilate (VEGFR2 small molecule tyrosine kinase inhibitor) are common antiangiogenic drugs for patients with late-stage gastric cancer.

For metastatic gastric adenocarcinoma/EGJ, which progressed after first-line platinum and/or fluorouracil-based chemotherapy, the REGARD study [35] showed that monotherapy with ramucirumab, compared with placebo, as a second-line treatment, can prolong mOS (5.2 vs. 3.8 months, P = 0.047).

The RAINBOW study [36] showed that, compared with paclitaxel alone, second-line ramucirumab in combination with paclitaxel can prolong mOS (9.63 vs. 7.36 months, P = 0.0169) and have tolerable adverse reactions, which led to the approval of ramucirumab alone or in combination with paclitaxel by the US FDA as a second-line treatment for stomach cancer at a late stage. Phase III clinical trial [37], which included 273 patients who had treatment failure after using second-line/follow-up chemotherapeutic regimens, showed that apatinib, compared with placebo, can prolong mPFS (2.6 vs. 1.8 months, P < 0.001) and increase the level of disease control (42.05% vs. 8.79%, P < 0.001).

Apatinib mesilate is approved for third or higher line treatment in patients with advanced gastric adenocarcinoma or EGJ. The CSCO Expert Committee on the Safety Management of Anticancer Drugs suggests using the guidelines "Expert Consensus on the Clinical Use of apatinib mesilate" to assist clinicians regarding the use and safety of apatinib [38].

According to the results of prospective clinical studies, immune checkpoint inhibitors have been approved for the treatment of third-line gastric cancer worldwide.

Regarding the treatment of Asian populations, the results of the ATTRACTION-2 study [39] showed that the risk of death in patients with recurrent or metastatic gastric or EGJ adenocarcinoma treated with nivolumab as a third-line treatment was significantly lower than that of placebo.

The indicators of one-year S of the two groups were 26.2% and 10.9%, respectively.

In 2020, updated 3-year follow-up data at ASCO-GI showed continued survival benefits for patients treated with the nivolumab group [40].

In March 2020, the NMPA of China approved the use of nivolumab for patients with progressive or recurrent gastric adenocarcinoma/EGJ who received two or more systemic treatment regimens.

The results of the study KEYNOTE-059 [41] showed that pembrolizumab as a third-line treatment for recurrent or metastatic gastric cancer adenocarcinoma / EGJ with PD-L1 CPS ≥ 1 had 6 months and an overall response rate (ORR) of 12%.

Currently, the use of PD-1 antibodies in Chinese clinical trials of advanced gastric cancer that failed with standard chemotherapy has demonstrated an ORR of 10%-20% and controlled safety.

For second-line treatment using immunotherapy for gastric cancer, a clinical trial that included 11 types of dMMR/MSI-H malignant tumors, including stomach cancer that had not undergone traditional treatment, showed that pembrolizumab treatment could be beneficial and was associated with ORR 53% and CR 21% [42].

The results of the study KEYNOTE-061 [43] showed that, compared with paclitaxel, second-line treatment with pembrolizumab did not lead to a significant prolongation of S in patients with PD-L1 CPS ≥ 1, although subsequent analysis showed that TMB

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and PD-L1 CPS were associated with the benefits of pembrolizumab, but pembrolizumab had a better safety profile than paclitaxel.

The status of immunosuppressants in the treatment of late-stage gastric cancer has not been confirmed, and it is not recommended to use immunosuppressants alone or in combination in normal practice. Patients are encouraged to participate in appropriate clinical trials.

The strategy of RV immunotherapy includes PD-1 mAb or a combination with chemotherapy. For combination therapy, there are three randomized controlled phase III trials in which PD-1 mAb was compared in combination with chemotherapy or chemotherapy alone.

The results of a phase III clinical trial of KEYNOTE-062 [4] showed that for patients with PD-L1 CPS ≥ 1, pembrolizumab in combination with chemotherapy (capecitabine or 5-fluorouracil + cisplatin) was not associated with a significant improvement in OS compared with chemotherapy alone.

The CheckMate-649 study [45] showed that for patients with PD-L1 CPS ≥ 5 mOS of combined chemotherapy with nivolumab (FOLFOX or XELOX) was longer than that of single chemotherapy (mOS: 14.4 vs. 11.1 months, risk ratio (HR) = 0.71, P < 0.0001); a significant survival advantage is also It was observed in the secondary endpoint group, which consisted of S in all randomized patients and patients with PD-L1 CPS 1 or higher. In addition, combination therapy demonstrated the benefit of PFS in patients with CPS ≥ 1 and in all randomized patients, as well as statistical significance in patients with CPS ≥5 (mPFS = 7.7 vs. 6.0 months, HR = 0.68, P < 0.0001). Thus, nivolumab in combination with FOLFOX/XELOX is recommended for late-stage gastric cancer with PD-L1 CPS ≥ 5.

ATTRACTION-4 clinical trial [46], a multicenter randomized phase II/III clinical trial evaluated the efficacy and safety of nivolumab plus chemotherapy (SOX/XELOX) compared with chemotherapy as a first-line treatment in patients with HER2-negative, progressive or recurrent gastric cancer/EGJ. The results of the study showed that mPFS of the nivolumab plus chemotherapy group significantly exceeded chemotherapy (10.5 vs. 8.3 months, HR = 0.68, P = 0.0007). In addition, the ORR and duration of response (DoR) of the nivolumab plus chemotherapy group were significantly higher than those of the chemotherapy group (ORR, 57.5% vs. 47.8%, P = 0.0088). However, it should be noted that the mOS of the two groups was similar (17.45 vs. 17.15 months, HR = 0.90), and in terms of ethnicity, only 5% of the participants were from Taiwan, China. For patients with unknown PD-L1 status, conventional therapy in combination with PD-1 mAb is not recommended.

For the first-line use of a single drug immunotherapy for gastric cancer, the KEYNOTE-059 study showed that in patients with PD-L1 CPS ≥ 1, pembrolizumab was associated with ORR 26%, DCR 36%, mPFS 3.3 months and mOS 20.7 months [41].

The phase III study of KEYNOTE-062 showed that in patients with PD-L1 CPS ≥ 1, pembrolizumab was not inferior to chemotherapy (10.6 vs. 11.1 months), but there was an intersection of their survival curves, and the risk of progression should be taken into account [44].

It was suggested that pembrolizumab should be considered only in patients with contraindications to chemotherapy or who have refused chemotherapy, and their health status and nutritional function should be carefully monitored. In the MSI-H subgroup, the ORR of the pembrolizumab group was 57.1% (compared to 36.8% with chemotherapy), and mOS was not achieved (NR) in both arms of pembrolizumab; for comparison, pembrolizumab compared to chemotherapy, mOS was NR (95% CI, 10.7 months-NR) versus 8.5 months (95% CI, 5.3-20.8 months), respectively, and mOS was NR (95% CI, 3.6 months-NR) with pembrolizumab plus chemotherapy compared to 8.5 months (95% CI, 5.3-20.8 months) with chemotherapy.

In addition, an analysis of Asian subgroups showed that pembrolizumab monotherapy was associated with superior survival benefits than chemotherapy, with an OV of 22.7 vs. 13.8 for patients with CPS ≥1 and 28.5 vs. 14.8 for patients with CPS <1. Due to the lack of sufficient data on the risk of excessive progression with pembrolizumab monotherapy, the use of one first-line drug immunotherapy is not recommended in patients with PD-L1 CPS ≥1, but may be considered if there are contraindications to chemotherapy. For patients with MSI-H, pembrolizumab monotherapy has shown obvious survival benefits compared to chemotherapy alone, and thus chemotherapy alone is not recommended in this patient group.

Currently, dMMR/MSI-H is recognized as a predictor of the effectiveness of immunotherapy in gastric cancer [42]. The US FDA has approved pembrolizumab and nivolumab as second- or third-line treatment for all patients with solid tumors with MSI-H or dMMR.

In addition to the above clinical studies, in which the PD-L1 CPS score was used as a screening criterion, the results of the KEYNOTE-061 study [43] showed that for patients with PD-L1 CPS ≥1, 5 and 10, compared with paclitaxel alone, pembrolizumab was

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associated with an extended OV of 0.8, 1.9 and 2.4 months accordingly, showing an association between PD-L1 CPS score and treatment response, which was also confirmed in the CheckMate649 study [164].

The KEYNOTE-061 study [43] also showed that in patients with high TMB, pembrolizumab was associated with higher ORR, PFS, and OS than paclitaxel. In a Chinese phase II study using toripalimab for the treatment of refractory gastric cancer, ORR (33.3% vs. 7.1%, P = 0.017) and OS (14.6 vs. 4.0 months, P = 0.038) of patients with high TMB (≥ 12 muts/Mb) were also significantly better than those with low TMB (<12 muts / Mb) [47].

In a prospective phase II clinical trial from Korea [48], which included 61 patients with metastatic gastric cancer treated with pembrolizumab as a life-saving treatment, patients with MSI-H or EBV-positive tumors showed dramatic responses to pembrolizumab (ORR 85.7% in metastatic gastric cancer MSI-H and ORR 100% in case of EB-positive metastatic stomach cancer).

Thus, the positivity of EBV in gastric cancer may be associated with a positive response to therapy with PD-1 antibodies. Nevertheless, two observational studies in the Chinese population showed that the effective frequency of patients with EB-positive gastric cancer receiving immunosuppressants was 33.3% [49, 50].

Therefore, the question of whether EBV infection can be used as a key marker for immunotherapy still needs to be confirmed in prospective studies.

Several phase II studies have shown that combination therapy using anti-HER2 drugs in combination with a PD-1 antibody or an antiangiogenic inhibitor in combination with a PD-1 antibody may be a potential treatment strategy in HER2-positive patients with gastric cancer; i.e. pembrolizumab plus trastuzumab in combination with XELOX for the treatment of first-line late-stage gastric cancer (NCT0365326, CTR20182551) [51], and camrelizumab in combination with XELOX followed by camrelizumab and apatinib as first-line therapy for progressive or metastatic gastric cancer or gastroesophageal junction [52].

Such regimens are currently still being investigated in phase III clinical trials (NCT03813784, CTR20200660) and are not recommended for routine clinical practice.

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