Advances in Treatment Models of Advanced Gastric Cancer

Tao Li[1,+], Yufang He[2,+], Qinglei Zhong[2,+], Jiang Yu[1], and Xinhua Chen[1] (iD)

Abstract

The prognosis of advanced gastric cancer (AGC) is extremely poor, and the therapeutic effect of traditional palliative chemotherapy is far from satisfactory. To overcome this bottleneck, palliative surgery resection, perioperative chemotherapy combined with surgical resection, hyperthermic intraperitoneal chemotherapy (HIPEC), pressurized intraperitoneal aerosol chemotherapy (PIPAC), radiation therapy, molecular-targeted therapy have been explored in AGC. Although considerable progress has been achieved, there is still no overwhelming therapeutic method. Due to the high heterogeneity of AGC, it is particularly vital to reshaped the paradigm of gastric cancer therapy according to the characteristics of clinical classifications and molecular subtypes.

Keywords

gastric cancer, cancer treatment, chemotherapy, HIPEC, conversion therapy, molecular-targeted therapy

Advanced gastric cancer (AGC) includes local unresectable GC, distant metastasis and postoperative recurrent GC.[1] At present, the main goal in treating AGC is to improve the symptoms and prolong the survival time of patients with sequential lines of chemotherapy.[2] However, the median survival time with this approach is only 4–13 months.[3,4] Although the treatment effect of AGC by systemic chemotherapy alone is gradually improving, the prognosis of AGC is far from expected. Thus, both more effective chemotherapy drugs and regimens with less toxic side effects and new treatment models should be explored. In this regard, various potential approaches have been studied: palliative surgery resection followed by postoperative adjuvant chemotherapy, preoperative chemotherapy and surgical resection, hyperthermic intraperitoneal chemotherapy (HIPEC), pressurized intraperitoneal aerosol chemotherapy (PIPAC), radiation therapy, molecular-targeted therapy. Overall, although considerable progress has been made, there is still no overwhelming treatment strategy for AGC at present. Due to the high heterogeneity of AGC, it is particularly important to screen subgroups sensitive to each treatment model to overcome this bottleneck. It requires a summary of the experience from current research and to further design reasonable and rigorous research for further exploration of potential solutions. Therefore, this paper reviews the progress made in treatment models for AGC.

1. Palliative Resection Followed by Postoperative Adjuvant Chemotherapy

Surgical removal of AGC is usually palliative. Theoretically, gastrectomy can reduce the tumor burden, improve symptoms such as obstruction and bleeding caused by advanced tumors, and improve patients' tolerance to chemotherapy. However, the suppression of immunity and the release of inflammatory factors, such as VEGF, IL-1β, IL-6, MCP-1, and TGC-β, caused by surgical excision can promote the growth and metastasis of residual tumors.[5] The surgery and potential postoperative complications may also lead to delaying chemotherapy timing, increasing adverse reactions to chemotherapy and reducing tolerance to chemotherapy.

A series of retrospective studies have shown that primary lesion excision, with or without metastasis excision, followed by postoperative adjuvant chemotherapy in patients with high selectivity, may prolong patient survival. High selectivity conditions include an age of less than 70 years with a single metastatic lesion, patients with liver metastasis who possess only one initial unresectable factor and respond well to chemotherapy, or patients with liver metastases that can be completely resected.[6–9] However, most studies are single-center studies with limited

[1] Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, China
[2] The First Clinical Medical School, Southern Medical University, Guangzhou, Guangdong, China

[+] Tao Li, Yufang He and Qinglei Zhong contributed equally to the work

Corresponding Author:
Dr Xinhua Chen, MD, PhD. Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China.
Email: xinhuachen03@163.com

samples and obvious case selection deviation. In addition, the enrolled patients often have a good physical status, few complications and a relatively limited tumor burden. Nevertheless, the prospective multicenter randomized controlled clinical trial REGATTA showed a contrasting result to the above retrospective studies. This study included 175 patients with a single unresectable metastatic factor who were randomly divided into chemotherapy alone (n = 86) and gastrectomy followed by chemotherapy (n = 89).[10] The operation was gastrectomy plus D1 lymph node dissection, without resection of the metastatic lesion. The results revealed that the median survival time in the chemotherapy alone group was 16.6 months, while that in the gastrectomy plus chemotherapy group was 14.3 months (P = 0.70), and the incidence of grade 3/4 adverse reactions in the surgery combined with chemotherapy group was higher than that in the chemotherapy alone group.[10] Therefore, the effect of surgical palliative resection combined with postoperative adjuvant chemotherapy on the survival improvement of AGC is still in dispute.

Based on the results of previous studies, to further explore the therapeutic benefits of surgery for AGC, the following must be fully considered in the study design: (1) patients undergoing surgical treatment must be selective; (2) the nature of the operation must be clear (either palliative or radical); and (3) importance must be attached to the use of preoperative systemic therapy.

2. Conversion Therapy

In recent years, researchers have focused on another mode of treatment, conversion therapy, for AGC. This treatment is aimed at those patients with GC that is initially unresectable but can potentially be surgically resected. After systemic therapy, the unresectable factors of these patients are partially or completely relieved, and R0 resection can be achieved to prolong postoperative and/or relapse-free survival time.[11–13] A patient scheduled to undergo conversion therapy demonstrates a good preoperative tolerance to systemic therapy, a sufficient dose of which causes the tumor to downstage to permit R0 resection, whereas residual tumor lesions after R1 or R2 resection would rapidly progress under the activation of inflammatory factors.[14] Conversion therapy first achieved success in the treatment of advanced colorectal cancer and has now become an important way to improve the long-term survival of patients with advanced colorectal cancer.[15] However, conversion therapy for GC is still at the initial stage of exploration.[12]

The efficacy and safety of conversion therapy have been preliminarily demonstrated in early, small-sample single-center studies.[11,16] With the improvement of chemotherapy regimens, a series of high-quality studies conducted by The Japanese Gastric Cancer Association have verified the feasibility of translational therapy.[17–19] The study by Kinoshita et al[20] included 57 patients with stage IV GC, and the results showed that after conversion therapy, 34 patients were able to undergo surgical resection. Compared with that of patients who did not undergo surgical excision, the median survival time of patients who underwent excision was significantly longer (29.9 months vs 9.6 months, P < 0.001), and no treatment-related deaths occurred. The results suggest that tumor resectability following preoperative chemotherapy is an important prognostic factor.[20] The results from Mieno et al[21] demonstrated that the median survival time of 31 patients was 56.1 months, and the R0 resection rate was 74.2%. Compared with patients who underwent R2 resection, patients who underwent R0 or R1 resection had a significant survival advantage (P < 0.001). This suggests that R0 resection is an important prognostic factor. In the prospective phase II AIO-FLOT3 trial, 60% (36/60) of patients with localized metastatic GC were treated with sequential surgery after 4 cycles of the FLOT regimen containing docetaxel, and the median postoperative survival time was 31.3 months (22.9 months in the whole group).[22] In 2019, the results of a meta-analysis of 23 studies by Du et al[23] showed that the 1-year (RR = 0.35; 95% CI 0.28-0.42; I2 = 45.3%, P < 0.001) and 3-year survival rates (RR = 0.63; 95% CI 0.54-0.74; I2 = 72.9%, P < 0.001) were significantly greater for operative treatment than for nonoperative treatment in patients with AGC after conversion therapy; postoperative survival was also significantly improved in patients who underwent R0 resection compared with patients who underwent R1–2 resection. At present, the conversion chemotherapy regimen tends to be a two-drug regimen based on cisplatin or a three-drug combination regimen based on docetaxel, for which the conversion safety and efficacy also tend to be improved (Table 1).

Since some AGC patients could benefit from conversion therapy vary greatly in clinical practice,[24,25] it is particularly important to explore which subgroups will benefit from conversion therapy. Therefore, a systematic classification of conversion therapy for AGC was proposed by Yoshida et al to guide the practice.[26,27] According to whether there was visible peritoneal metastasis, AGC was first classified into 2 categories and further divided into 4 categories according to metastasis to other organs and resectability of the tumor. Category 1 includes patients without apparent peritoneal disease and technically resectable metastatic lesions; Category 2 includes patients without apparent peritoneal disease but whose metastatic lesions are technically unresectable or can potentially be removed; Category 3 includes patients with macroscopic peritoneal dissemination and whose metastatic lesions cannot be radically removed; and Category 4 includes patients with macroscopic peritoneal dissemination with unresectable metastatic lesions. Then they investigated 283 stage IV gastric cancer or esophageal stomach cancer patients by using this classification method, and the results showed that conversion therapy is safe and feasible. There were significant differences in survival time between patients who underwent conversion surgery and those who did not in different groups. This preliminary data proves that this classification method has certain clinical guiding significance and can provide a reference for the clinical classification of AGC. On this basis, a international retrospective cohort study was conducted (CONVO-GC-1) to explore the application of conversion surgery in the treatment of advanced gastric cancer, which again supported the above conclusions and provided a

Table 1. Comparison of conversion protocols, efficacy and safety of conversion therapy for gastric cancer

First author	Year	Inclusion criteria	Chemotherapy regimens	Patients treated with conversion therapy	3-year survival rate (%)	5-year survival rate (%)	Total median survival time (months)	Median survival time(R0resection/no R0 resection) (months)	R0 removal rate (%)	Treatment-related deaths/total number of patients treated
NakajimaT[11]	1997	Unresectable IV stage GC	FLEP	30	-	-	6.5	-	30%	4/30
YanoM[16]	2002	Unresectable GC	FEMTXP or THP-FLPM	33	-	-	-	-	24.2%	1/33
Yoshikawa T(JCOG0001)[17]	2009	Locally GC with extensive LNM	Irinotecan plus cisplatin	55	27	-	14.6	-	65	3/55
SatohS[19]	2011	Stage IV GC	CS	51	-	-	19.2	-	51	0/51
Tsuburaya A (JCOG0405)[18]	2014	Locally GC with extensive LNM	CS	51	59	53	-	-	82	0/52
KinoshitaJ[20]	2015	Unresectable IV stage GC	DCS	57	50.1	-	-	29.9/9.6	47.4	0/57
MienoH[21]	2017	GC cannot be resected initially	DCS	31(surgical cases only)	-	-	56.1	-	74.2	0/31
SatoY[24]	2017	GC cannot be resected initially	DCS	100	-	-	21.7	47.9/21.7	28	0/100
Salah-EddinA (AIO-FLOT3)[22]	2017	Localized metastatic GC	FLOT	60	-	-	22.9	-/-	-	0/60

GC: Gastric cancer. LNM: lymph node metastasis. FLEP: 5-fluorouracil, leucovorin, cisplatin, etoposide.FEMTXP: 5-fluorouracil, leucovorin, cisplatin, pharmorubicin, methotrexate, cisplatin.
THP-FLPM: Pirarubicin, 5-fluorouracil, calcium leucovorin, cisplatin, mitomycin C.CS: cisplatin plus S-1.DCS: Docetaxel, cisplatin and S-1. FLOT: Docetaxel, oxaliplatin, calcium leucovorin and 5-fluorouracil.

foundation for further prospective studies.[28] Based on the current level of clinical diagnosis and the difficulty and risk of treatment, Jiafu Ji *et al* classified AGC based on surgery orientation after clinical assessment into the resectable type and the unresectable type, to help better perform clinical practice.[29]

Incouragingly, some studies have showed that apatinib combined with dual drug chemotherapy (S-1, paclitaxel) presented higher rates of conversion and R0 resection and a superior survival benefit in unresectable AGC.[30,31] At present, molecular-targeted therapy have shown great potential in the treatment of AGC, which can open up a potential new clinical path for the conversion therapy of stage IV GC.

3. Local Chemotherapy

For GC patients with peritoneal metastasis, due to the existence of the peritoneal plasma barrier and the low concentration of drugs in the abdominal cavity, it is difficult to achieve effective cytotoxic effects on metastatic foci. Therefore, direct local intraperitoneal administration has become an important adjunct to systemic chemotherapy and surgery. Some phase II clinical trials confirmed the safety and benefit of S-1 combined with paclitaxel intraperitoneal perfusion chemotherapy.[32,33] With the thermotherapy effect of hyperthermia and its synergistic effect on cytotoxicity, HIPEC enhances not only the absorption of drugs in abdominal metastatic foci but also the efficacy of cytotoxic drugs in killing tumor cells. In recent years, due to the improvement of constant temperature and circulatory perfusion systems, their safety has been constantly improved.[32] Therefore, scholars are actively exploring the benefits of HIPEC in the above treatment model for AGC. In 1988, Fujimoto *et al*[34] first reported the application of palliative surgical resection combined with HIPEC in patients with peritoneal metastatic carcinoma of gastric cancer and confirmed its safety. In 1996, Yonemura *et al*[35] reported a cohort study on palliative surgical resection combined with HIPEC and showed that 83 patients with peritoneal metastatic cancer had a 5-year survival rate of 11%, which confirmed that some select patients could benefit substantially from this treatment model. Subsequently, the survival benefit and safety of palliative surgical resection combined with HIPEC were reported in Eastern and Western countries.[36–39] In a randomized controlled phase III clinical study conducted by Yang *et al*[36] in 2011, 68 AGC patients with peritoneal metastasis were randomly divided into the cytoreductive surgery plus HIPEC group and the cytoreductive surgery alone group. The peritoneal metastasis score and tumor reduction degree of the two groups were basically the same. Compared with the cytoreductive surgery group alone, the median survival time of patients in the cytoreductive surgery plus HIPEC group was significantly improved (11.0 months vs 6.5 months, $P = 0.046$), while the incidence of serious adverse events was not significantly different (14.7% vs 11.7%, $P = 0.839$). The CYTO-CHIP study[39] collected 277 consecutive GC patients with peritoneal metastasis from 1989 to 2014 across 19 centers in France, among whom 180 received cytoreductive surgery plus HIPEC versus 97 who only received

cytoreductive surgery. An inverse probability-weighted Cox proportional hazard regression model based on the propensity score was used, and multivariate model and sensitivity analysis were also performed. The results demonstrated that, compared with cytoreductive surgery alone, cytoreductive surgery plus HIPEC could remove free cancer cells and residual small tumor lesions and safely and effectively improve prognosis.

In recent years, PIPAC and its modified type, hyperthermic pressurized intraperitoneal aerosol chemotherapy (H-PAC), have been expected to provide a more effective treatment for advanced patients with peritoneal metastasis.[40,41] In theory, PIPAC and H-PAC can overcome the shortcomings of weak penetration of HIPEC chemotherapy drugs to peritoneal nodules and low peritoneal diffusion,[42,43] but there remains a lack of real effective evidence.

4. Radiation Therapy

Currently, radiotherapy is rarely used in the treatment of AGC. The existing preliminary research results show that radiotherapy can play a certain auxiliary role in surgical treatment or palliative chemotherapy for AGC.[44–49] For patients with inoperable cancer, radiotherapy combined with chemotherapy can improve symptoms of discomfort. For patients undergoing palliative surgery, preoperative radiotherapy can play a role in tumor downstaging. Intraoperative radiotherapy can kill certain cancer cells or tissue remaining after surgical resection. Moreover, since irradiation can directly and precisely reach the surface of tumor tissues, the radiation absorbed dose can be increased. However, attention should be paid to the effect on adjacent organs such as the duodenum, jejunum and pancreas. Postoperative radiotherapy can reduce the postoperative recurrence rate or metastasis rate to a certain extent.[50–52]

5. Molecular-Targeted Therapy

Targeted therapy is an emerging therapeutic approach that targets some specific landmark molecules overexpressed by tumor cells and selects targeted blocking agents to intervene in the signal transduction pathways closely related to tumorigenesis and development to inhibit tumor proliferation, growth, invasion and metastasis. Targeted agents, including human epidermal growth factor receptor 2 (HER2), inhibitors of angiogenesis, mesenchymal-epithelial transition, epidermal growth factor receptor, mammalian target of rapamycin, claudin-18.2, DNA and programmed death-1(PD-1).

The significant milestone of molecular-targeted therapy is ToGA trial, a prospective multicenter randomized phase III clinical trial in 2010. ToGA trial enrolled 594 advanced gastric or gastroesophageal junction cancer(GC/GEJC) patients who were HER2-positive and randomly divided them into a trastuzumab plus chemotherapy group (n = 298) and a chemotherapy alone group (n = 296). The chemotherapy regimen was capecitabine plus cisplatin or fluorouracil plus cisplatin. The results showed that the median progression-free survival

times in the trastuzumab plus chemotherapy group and the chemotherapy alone group were 6.7 months and 5.5 months, respectively. The median overall survival was 13.8 months and 11.1 months, respectively. The differences between the two groups were statistically significant.[53] ToGA laid the foundation for trastuzumab as the first-line treatment for HER2-positive GC. Based on this trial, trastuzumab was subsequently used for clinical treatment. Furthermore, the recently published results of a phase 2 clinical trial, the DESTINY-Gastric-1 trial,[54] evaluated patients with unresectable or metastatic HER2-positive GC and gastroesophageal junction adenocarcinoma using the HER2 antibody-conjugated drug (ADC) DS-8201. Encouragingly, both the primary and key secondary endpoints of DESTINY-Gastric-1 trial met the expected standards. Compared with chemotherapy (paclitaxel or irinotecan), DS-8201 improved the overall response rate and prolonged the overall survival time of patients with advanced HER2-positive G/GEJ adenocarcinoma treated as third-line and above treatment. This study provides a reliable alternative solution to drug resistance in patients with HER2-positive GC/GEJC .

Relevant clinical trials conducted in the field of targeted therapy for GC also include targeted drugs for inhibitors of angiogenesis, mesenchymal-epithelial transition, epidermal growth factor receptor, mammalian target of rapamycin, claudin-18.2, DNA and immune checkpoint inhibitors (ICIs) etc(Table 2). And as we are witnessing a signifcant change of treatment landscape, patients with AGC are having more treatment options available and living longer since clinical trial incorporating targeted agents. Among the molecular-targeted therapy, ICIs reshaped the management of GC most profoundly.

Tumor cells are able of evading host immune clearance via downregulating T-cell

immune responses. This process is mediated by activation of immune checkpoints such as cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), PD-1 and PD-L1.[55] Encouragingly, blocking PD-1/PD-L1 axis by ICIs have shown potential promisssing results for GC. In 2016, KEYNOTE-012 study opened the way to immunotherapy for AGC. KEYNOTE-012 was a phase 1b multicohort umbrella trial involving head and neck tumors and breast, gastric, urothelial and other cancers.[56] In the GC cohort, pembrolizumab monotherapy (10 mg/kg) was as good as or better than third-line therapy for PD-L1-positive AGC patients (including those from the USA, Japan, South Korea and Taiwan). 8 out of 36 patients were judged to have had an overall response. The median progression-free survival (PFS) time was 1.9 months, and the median overall survival (OS) time was 11.4 months. The 6-month PFS rate was 24%, and the 6-month OS rate was 69%. The incidence of grade 3–4 adverse reactions was 13% without treatment-related death. KEYNOTE-012 trial confirmed that pembrolizumab has considerable antineoplastic activity and manageable treatment-related side effects in AGC for the first time. Subsequently, Fuchs CS et al[57] carried out a global multicenter, multicohort phase II trial (KEYNOTE-059), exploring the

effect of pembrolizumab (200 mg) for AGC patients who had failed in previous treatment. KEYNOTE-059 was divided into three cohorts: ① cohort 1, patients with metastatic GC (PD-L1 positive or negative), who had previously received more than second-line chemotherapy and were here administered monotherapy with pembrolizumab; and ② cohort 2 and cohort 3, who were administered first-line combination therapy with pembrolizumab and chemotherapy for newly diagnosed patients with metastatic GC and monotherapy with pembrolizumab, respectively. Primary endpoints were safety (cohorts 1, 2, and 3) and objective response rate (cohorts 1 and 3). The results for cohort 1 showed that[57] ORR rate was 11.6%, with a complete response of 2.3%. The median PFS was 2.0 months, with a 6-month PFS rate of 14.1%. While the median OS was 5.6 months, with a 6-month OS rate of 46.5%. The ORR of PD-L1-positive patients was higher than that of PD-L1-negative patients (15.5% vs 6.4%). During the same period, the parallel multicenter randomized controlled trial (ATTRACTION-2)[58] ,which was design to observe the efficacy and safety of nivolumab (3 mg/kg q2w) compared with placebo in the treatment of advanced gastric cancer at or above the third line. Its results showed that the OS of patients in the nivolumab group was significantly better than that in the placebo group. The incidence of grade 3–4 adverse reactions in nivolumab group was 34%. In 2020, ASCO-GI updated the OS and PFS results of ATTRACTION-2 follow-up for 3 years. For the primary endpoint, OS, the treatment of nivolumab reduced the risk of death by 38%, and the benefit reflected a long-term trend.[59] The 1-year, 2-year and 3-year survival rate of the nivolumab treatment group were significantly better than those of the placebo group. Among all the patients enrolled in the group, the 3-year OS rate and 3-year PFS rate in the nivolumab group were still significantly higher than those in the control group (5.6% vs 1.9%, 2.4% vs 0). There were 15 and 3 patients in the two groups who survived for more than 3 years, respectively, and 2 of the 3 patients in the control group received nivolumab treatment.

Unfortunately, however, in subsequent clinical trials in which immunotherapy were moved to second-line treatment for AGC, the results of the KEYNOTE-061 trial puzzled clinicians.[60] The KEYNOTE-061 trial was a phase III, multicenter, randomized controlled trial investigating pembrolizumab versus paclitaxel as second-line therapy in the treatment of GC/GEJC. The primary endpoint was PFS in people with a CPS of 1 or higher.[60] Among the 395 patients with a CPS of 1 or higher, the median OS was 9.1 months with pembrolizumab and 8.3 months with paclitaxel. The median PFS was 1.5 months with pembrolizumab and 4.1 months with paclitaxel. As a second-line therapy, pembrolizumab monotherapy has no advantage over paclitaxel chemotherapy.

Although the results of the second-line study may be confusing, the researchers did not stop pursuing the use of immunotherapy as a first-line therapy for AGC. The cohort 2 data from KEYNOTE-059 trial showed that the ORR after first-line treatment with pembrolizumab plus cisplatin and 5-FU

Table 2. Presented phase III trials with targeted agents in advanced gastric cancer

Target	Trial	Agent	Trial design	Overall survival benfit
HER 2	ToGA[53]	Trastuzumab1/ first- line	Chemotherapy with or without trastuzumab	Positive
Angiogenesis	REGARD[74]	Ramucirumab/ second and third-line	Ramucirumab versus placebo	Positive
	RAINBOW[75]	Ramucirumab/ second-line	Paclitaxel with ramu- cirumab or placebo	Positive
	AVAGAST[76]	Bevacizumab/ first-line	Chemotherapy with bevacizumab or placebo	Negative
	AVATAR[77]	Bevacizumab/ first-line	Chemotherapy with bevacizumab or placebo	Negative
MET	RILOMET-1[78]	Rilotumumab/ first-line	mFOLFOX6 with rilotumumab or placebo	Negative
	METGastric[79]	Onartuzumab/ first-line	mFOLFOX6 with onartuzumab or placebo	Negative
EGFR	EXPAND[80]	Cetuximab/ first-line	Chemotherapy with or without cetuximab	Negative
mTOR	GRANITE-1[81]	Everolimus/ third-line	Everolimus versus placebo	Negative
Claudin-18.2	SPOTLIGHT[82]	IMAB362/ first-line	IMAB362 plus mFOLFOX6 versus placebo plus mFOLFOX6	Ongoing
PARP	GOLD[83]	Olaparib/ second-line	Paclitaxel with olaparib or placebo	Negative
DNA	TAGS[84]	TAS-102/ third-line	TAS-102 versus placebo	Positive
PD-1/PD-L1	ATTRACTION-2[58]	Nivolumab /third-line	Nivolumab versus placebo	Positive
	KEYNOTE-061[60]	Pembrolizumab/ second-line	Pembrolizumab versus paclitaxel	Negative
	KEYNOTE-062[62]	Pembrolizumab/ first-line	Pembrolizumab alone or pembrolizumab plus chemotherapy versus chemotherapy alone	Noninferior for Pembrolizumab
	CheckMate649[63]	Nivolumab /first-line	Nivolumab plus chemotherapy versus chemotherapy alone	Positive

HER2 human epidermal growth factor receptor 2, MET mesenchymal-epithelial transition, EGFR epidermal growth factor receptor, mTOR mammalian target of rapamycin, PARP poly (ADP-ribose) polymerase, DNA deoxyribonucleic acid, mFOLFOX6 5-fluorouracil/leucovorin/oxaliplatin, PD-1 programmed death-1, PD-L1 programmed death ligand 1.

or capecitabine in 25 unscreened, newly diagnosed AGC patients reached 60%.[61] And the ORR was 69% in PD-L1 + patients and 38% in PD-L1- patients. The median OS was 13.8 months and the median PFS was 6.6 months. Based on the high ORR results in the KEYNOTE-059 cohort, the researchers further conducted the KEYNOTE-062 trial.[62] A total of 763 patients with untreated, advanced GC/GEJC with PD-L1 CPS of 1 or greater were randomized 1:1:1 to pembrolizumab, pembrolizumab plus chemotherapy (cisplatin plus fluorouracil or capecitabine), or chemotherapy plus placebo. However, the results of the KEYNOTE-062 trial[62] showed that the combination of pembrolizumab and chemotherapy was not superior to chemotherapy alone as a first-line treatment[OS in patients with CPS of 1 or greater (12.5 vs 11.1

months; HR, 0.85; 95% CI, 0.70-1.03; P = .05) ;PFS in patients with CPS of 1 or greater (6.9 vs 6.4 months; HR, 0.84; 95% CI, 0.70-1.02; P = 0.04)]. The benefit of pembrolizumab was limited to PD-L1-positive patients, that is, patients with a CPS ≥ 10. Gratifyingly, however, recently the randomized, global phase III study, checkmate-649 trial[63] shown promise results in the administration of immunotherapy as a first-line treatment for AGC. This study evaluated the efficacy of nivolumab plus chemotherapy (XELOX or FOLFOX) or nivolumab plus ipilimumab in the treatment of patients with previously untreated, unresectable or metastatic gastric cancer, gastroesophageal junction cancer or esophageal adenocarcinoma (GC/GEJC/EAC) compared with chemotherapy alone. The results showed that the endpoint of PFS was

reached in patients with PD-L1 CPS≥ 5, CPS ≥ 1 and the all-randomized population. The PFS of nivolumab plus chemotherapy was significantly improved when compared with chemotherapy (PD-L1 CPS ≥ 5: 7.7 months vs 6.0 months, HR = 0.68, 95% CI 0.56-0.81; PD-L1 CPS ≥ 1: 7.5 months vs 6.9 months, HR = 0.74, 95% CI 0.65-0.85; whole population: 7.7 months vs 6.9 months, HR = 0.77, 95% CI 0.68-0.87). For patients with PD-L1 CPS ≥ 5, CPS≥ 1 or the all-randomized population, all presented a benefit in OS from nivolumab plus chemotherapy compared with chemotherapy alone (PD-L1 CPS ≥ 5: 14.4 months vs 11.1 months, HR = 0.71, 95% CI 0.59-0.86; PD-L1 CPS ≥ 1: 14.0 months vs 11.3 months, HR = 0.77, 95% CI 0.64-0.92; all-randomized population: 13.8 months vs 11.6 months, HR = 0.80, 95% CI 0.68-0.94). In terms of safety, the incidence of adverse events in the nivolumab plus chemotherapy group was similar to that in the chemotherapy group. There was no increase in the toxicity spectrum of immunotherapy combined with chemotherapy.

Interestingly, recently some research indicated that the scheduling of chemotherapy and immunotherapy, which is something not considered in the trials mentioned above, could also greatly affected the effect of immunotherapy. The presentation in ASCO (2021) has indicated the scheduling of chemotherapy and anti-PD-L influence the efficiency of immunochemotherapy in locally advanced esophageal squamous cell cancer.[64] The mechanisms included that chemotherapy can enhance tumor antigen presentation by upregulating the expression of tumor antigens themselves, or of the MHC Class I molecules to which the antigens bind. Alternatively, chemotherapy may upregulate co-stimulatory molecules or downregulate co-inhibitory molecules expressed on the tumor cell surface, enhancing the strength of effector T cell activity. Chemotherapy may also render tumor cells more sensitive to T cell-mediated lysis through different mechanisms.[65]

Surprisingly, the recent Japanese clinical phase II EPOC1706 trial[66] found that immunotherapy plus antivascular therapy demonstrated amazing results. A total of 29 patients with recurrent or metastatic GC were enrolled in the trial, of whom 14 were in the first-line setting and 15 were in the second-line setting. The results showed that the ORR rate of the antivascular regimen of pembrolizumab plus lenvatinib in the first-line and second-line treatment of GC was as high as 69%. In addition, biochemical markers such as PD-L1 expression and tumor mutation burden (TMB) were analyzed. ORR and PFS were significantly higher in patients with PD-L1 positivity (CPS ≥ 1), especially in patients with PD-L1 CPS ≥ 10, but there was no significant correlation between TMB and PFS. In terms of safety, grade 3 treatment-related adverse events occurred in 48% of patients. The most common was hypertension (11 patients, 38%), but all adverse events were resolved by dose adjustment, symptomatic medication and so on. The safety of combined therapy was also guaranteed, which provides a new perspective and hope for the use of immunotherapy in GC.

6. Conclusions

There is still no satisfactory treatment strategy for AGC.[67–69] Luckily, with persistent effort, new treatment models of AGC, especially conversion therapy and immunotherapy, have brought a new sense of hope and vision. Taking into consideration the high heterogeneity of GC [70–73], it is particularly important to further screen subgroups sensitive to each treatment model to develop individual and tailored treatments for AGC. Meanwhile, how to improving the response to immunotherapy and overcome drug resistance via tumor micro-environment changes caused by immunotherapy and chemotherapy are also future research directions.

Declaration of Conflicting Interests

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ORCID iD

Xinhua Chen https://orcid.org/0000-0002-1879-4318

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