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REVIEW ARTICLE

Global chemotherapy development for gastric cancer

Kazuto Harada[1] · Dilsa Mizrak Kaya[1] · Yusuke Shimodaira[1] · Jaffer A. Ajani[1]

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Abstract To combat the dismal mortality rates from metastatic gastric adenocarcinoma (GAC), new drugs and treatment strategies are needed. Today, metastatic GAC is predominantly treated by empiric chemotherapy. Combination of two cytotoxic agents has become commonplace in North America, Europe, and Asia. Human epidermal growth factor 2 (HER2) overexpression (protein or gene copy numbers) has resulted in the addition of trastuzumab in the first-line chemotherapy combination in patients whose tumor is HER2 positive. The addition of trastuzumab in this select population has provided a modest survival advantage. In this review we trace the global development of systemic therapy in patients with metastatic GAC and ponder what lies in the future.

Keywords Gastric adenocarcinoma · Chemotherapy · Molecularly targeted drug

Introduction

Gastric adenocarcinoma (GAC) is estimated to be the fifth commonest cancer in the world (951,000 cases), and the third leading cause of cancer deaths worldwide (723,000 deaths) [1]. More than 70 % of GAC cases occur in developing countries, particularly in East Asia [1]. The highest estimated mortality rates occur in East Asia (14.0 per 100,000 men, 9.8 per 100,000 women); the lowest are reported in North America (2.8 per 100,000 men, 1.5 9 per 100,000 women) [1]. The 5-year survival rate of GAC patients is 68.9 % in Japan [2], and 30.4 % in the USA; the latter results were reported in the Surveillance, Epidemiology, and End Results (2006–2012) database of the National Cancer Institute.

Despite the development of multimodality therapies such as surgery, chemotherapy, and radiation therapy, the mortality rates from metastatic GAC remain dismal. The median survival time of metastatic GAC patients is 9–10 months [3]. Today, metastatic GAC is mainly treated with empiric chemotherapy. The first major development was treatment with 5-fluorouracil (5-FU) alone or in combination with other agents, and these produced modest benefits over best supportive care [4–6]. After a lengthy period of approximately 30 years of slightly different approaches in North America, Europe, and Asia, we have reached a general global consensus for therapy recommendations for patients with metastatic GAC (Fig. 1). There have been parallel efforts to define the molecular underpinnings of GAC. Here we characterize some of the molecular biology, trace the global development of systemic therapy, and briefly describe new developments in the field.

Genomic profiling in gastric cancer

The current classification system for GAC is the Lauren classification, which divides GAC into two histological subtypes (intestinal and diffuse) [7]. The genome characterization of GAC has recently revealed four molecular genotypes that may help personalize therapy.

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✉ Jaffer A. Ajani
jajani@mdanderson.org

[1] Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd (FC10.3022), Houston, TX 77030, USA

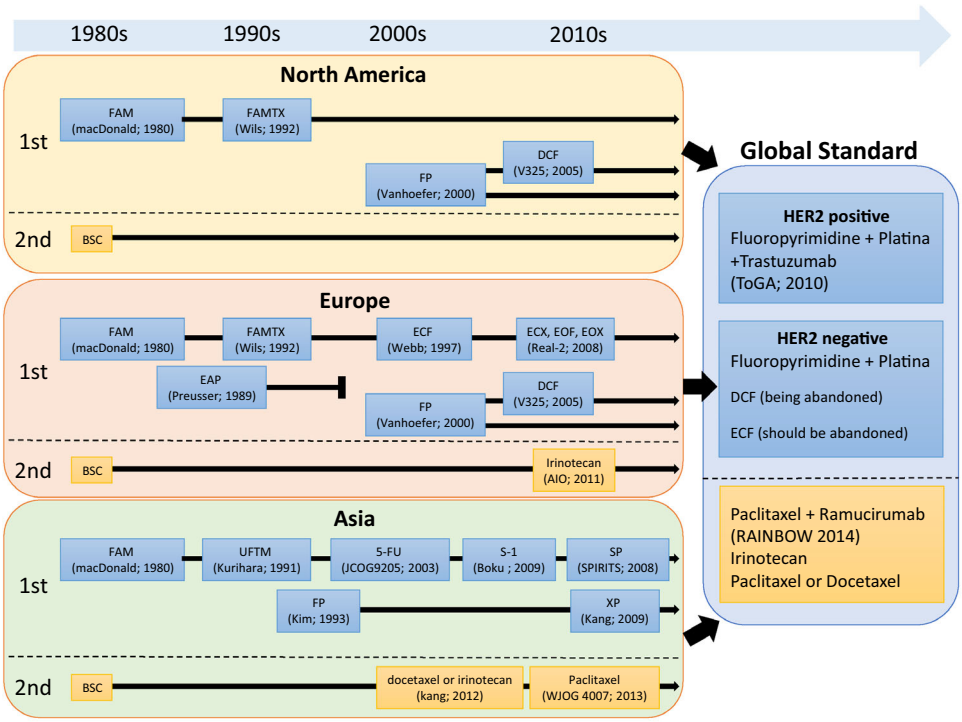

Fig. 1 Different approaches in North America, Europe, and Asia and general global consensus for therapy recommendations for patients with metastatic gastric adenocarcinoma. *BSC* best supportive care, *DCF* docetaxel, cisplatin, and intravenously administered 5-fluorouracil, *EAP* etoposide, adriamycin, and cisplatin, *ECF* epirubicin, cisplatin, and venous infusion of 5-fluorouracil, *ECX* epirubicin, cisplatin, and capecitabine, *EOF* epirubicin, oxaliplatin, and 5-fluorouracil, *EOX* epirubicin, oxaliplatin, and capecitabine, *FAM* 5-fluorouracil, doxorubicin, and mitomycin, *FAMTX* 5-fluorouracil, adriamycin and methotrexate, *FP* 5-fluorouracil and cisplatin, *5-FU* 5-fluorouracil, *HER2* human epidermal growth factor 2, *SP* S-1 and cisplatin, *UFTM* tegafur–uracil and mitomycin C, *XP* capecitabine and cisplatin

First, the Cancer Genome Atlas Research Network discovered that 295 primary GACs could be assigned to four molecular genotypes [Epstein–Barr virus (9 %), microsatellite instability (MSI) (22 %), genomically stable (20 %), and chromosomal instability (50 %)] [8]. Epstein–Barr virus associated cancer is characterized by hypermethylation of DNA promoters. In addition, *PIK3CA* and *ARID1A* mutations were identified in 80 and 55 % of GACs respectively. The amplification of the *JAK2* (Janus kinase) and *PDL1* genes was also detected in this group. In the second subtype, MSI is enhanced by mismatched-repair gene silencing, inducing frequent mutation of *PIK3CA* (42 %), *ERBB3* (14 %), *JAK2* (11 %), *EGFR* (5 %) and *HER2* (3 %). Thus, MSI tumors are associated with potential activation of the epidermal growth factor receptor (EGFR)–mitogen -activated protein kinase and phosphatidylinositol 3-kinase pathways. The third subtype is genomically stable, with adhesion and alterations of the cell migration genes *RHOA* (15 %) and *CDH1* (26 %), and fusion of *CLDN18* and ARHGAP genes(15 %). The fourth subtype, chromosomal instability, is characterized by frequent *TP53* mutations, and amplifications of *HER2* (24 %), *KRAS/NRAS* (18 %), *EGFR* (10 %), *PIK3CA* (10 %), *ERBB3* (8 %), *FGFR2* (8 %), and *MET* (8 %). This subtype primarily occurs in the proximal stomach.

The Asian Cancer Research Group recently discovered four genotypes [MSI (23 %), microsatellite stable (MSS)/epithelial–mesenchymal transition (EMT) (15 %), MSS/*TP53* negative (36 %),and MSS/*TP53* positive (26 %)] [9]. In MSI tumors, loss of *MLH1* expression is associated with frequent mutations in genes such as *ARID1A* (44.2 %), *KRAS* (23 %), and *ALK* (16.3 %). This subtype is also associated with antral cancers (75 %), and with an intestinal subtype (60 %). Among the four subtypes categorized by the Asian Cancer Research Group, the MSI subtype has the most favorable prognosis. The MSS/EMT subtype is characterized by MSS tumors with loss of E-cadherin. This subtype, which is likely to diffuse, exhibits the worst prognosis and a lower mutation rate than the others. Finally, the MSS/*TP53*-positive and MSS/*TP53*-negative subtypes are two forms of MSS epithelial tumors with different *TP53* activations. The MSS/*TP53*-negative subtype is characterized by frequent *TP53* mutations and chromosomal instability, whereas the MSS/*TP53*-positive subtype exhibits frequent mutations of *APC*, *ARID1A*, *KRAS*, *PIK3CA*, and *SMAD4*.

Differences between Western and Asian GACs

The molecular and clinical features of GAC seem to differ by region. In Asia, especially in Japan and Korea, distal gastric cancers are common because of the high frequency of chronic *Helicobacter pylori* infection [10, 11]. In Western societies, proximal gastric cancers are prevalent, and presumably result from gastroesophageal reflux disease and obesity [12, 13]. The prognosis of GAC has been more favorable in Asia than in the West. Whereas the 5-year survival rate of GAC is 68.9 % in Japan [2], the Surveillance, Epidemiology, and End Results (2006–2012) database of the National Cancer Institute reported a 5-year survival rate of 30.4 % in the USA. The GAC survival rates tend to increase in high-incidence regions [14], although high frequency of proximal GAC is correlated with unfavorable prognosis [15]. The different molecular features of Asian and Western cases might also influence the prognosis [8, 9]. In addition, the screening strategy in East Asia facilitates early detection and better prognosis [16, 17]. Moreover, intestinal type is commoner in Asia and poorly differentiated phenotypes (including the diffuse type) are commoner in the West. Importantly, human epidermal growth factor 2 (HER2) tumor expression is more frequent in the intestinal type than in the diffuse type [18–20].

These differences have warranted different treatment strategies. For instance, adjunctive therapy has differed in different regions [21–24].

Systemic therapy for metastatic GAC in the West

The first chemotherapeutic agent against metastatic GAC was 5-FU, either alone or in combination with various reagents. In the USA, initially 5-FU, doxorubicin, and mitomycin (FAM) was the standard therapy for metastatic GAC [25]. In the 1990s, a phase III multicenter trial in the EU demonstrated the superior performance of the 5-FU, adriamycin, and methotrexate (FAMTX) regimen over FAM [26]. Etoposide, adriamycin, and cisplatin (EAP) became temporarily popular in the 1990s, but was discontinued because it was significantly more toxic than FAMTX and conferred no survival benefit over FAMTX [27]. In the late 1990s, a randomized trial showed that epirubicin, cisplatin, and venous infusion of 5-FU (ECF) was better than FAMTX, which performed poorly in that trial [28]. ECF became popular especially in the EU, but it also remained controversial [29]. 5-FU-based or cisplatin-based combinations were considered as an acceptable standard therapy [30]. Additional phase III trials help evolve today's accepted standards. The first global randomized study was V-325 in 2006. It showed statistical superiority of docetaxel, cisplatin, and intravenously administered 5-FU (DCF) in terms of overall survival over cisplatin and 5-FU [3, 31]. However, as DCF produced many toxic effects, many modifications were developed. The original DCF is not recommended by the National Comprehensive Cancer Network guidelines. In 2000, new drugs such as capecitabine, oxaliplatin, and irinotecan were developed. Capecitabine, an orally administered fluoropyrimidine, is converted to 5-FU in cancer cells by thymidine phosphorylase [32]. Oxaliplatin is a third-generation diaminocyclohexane platinum compound, which (unlike cisplatin) is easy to administer but can cause significant neuropathy. The REAL-2 trial supported the noninferiority of capecitabine versus 5-FU and cisplatin versus oxaliplatin. [33]. Capecitabine plus cisplatin or capecitabine plus oxaliplatin has gained or retained popularity [34, 35]. Trastuzumab is added to the first-line cytotoxic therapy in patients with HER2-positive GAC [20].

The recommended first-line therapy for patients with good performance status is a two-drug combination of oxaliplatin plus 5-FU, S-1 (in the EU), or capecitabine. Irinotecan in the first-line setting did not produce a survival advantage and is used only rarely in this setting [36, 37].

Systemic therapy for metastatic GAC in Asia

In the 1980s, several phase II trials were performed in Japan. A randomized study comparing tegafur plus mitomycin C (FTM) and tegafur–uracil plus mitomycin C (UFTM) demonstrated a higher response rate with UFTM than with FTM [38]. Three studies investigated the efficacy of doxifluridine plus cisplatin, EAP, and 5-FU plus cisplatin [39, 40]. Among these, the JCOG9205 trial showed no survival benefit from 5-FU plus cisplatin and UFTM over 5-FU alone, indicating fluoropyrimidine as the standard first-line chemotherapy [41]. Different from Western therapies, the orally administered fluoropyrimidine S-1 has been developed in Asia, and is especially used in Japan [42]. In a phase III trial, S-1 was not inferior to 5-FU, so became the first-line therapy until SPIRITS showed that S-1 plus cisplatin was superior to S-1 alone [37, 43]. Currently, S-1 plus cisplatin is the standard first-line therapy in Japan and its use might expand [44]. Even in the West, S-1 was reported to be as effective as infusional 5-FU [45], but with a better toxicity profile. A combination of irinotecan and S-1 was not considered better than S-1 alone [46]. Capecitabine proved to be an acceptable therapy in two trials [34, 47]. In Japan, where S-1 is favored, capecitabine was not approved until the AVAGAST and ToGA studies confirmed the effectiveness and tolerability

of capecitabine plus cisplatin in Japanese patients [48]. S-1 combined with oxaliplatin appears to be as effective as S-1 combined with cisplatin. Thus, S-1 plus oxaliplatin is a suitable replacement for S-1 plus cisplatin [49]. In summary, the recommended first-line treatment for East Asian patients with HER2-negative tumors is a doublet regimen of a fluoropyrimidine plus a platinum drug, such as capecitabine plus cisplatin, S-1 plus cisplatin, or capecitabine plus oxaliplatin. DCF was used in China, India, South Korea, and Taiwan, but its use is limited to relatively healthy patients. Epirubicin was never popular in many Asian countries.

We have witnessed globalization of many pivotal trials in GAC because of the acceptance of reference regimen(s), particularly in the first line.

Global perspectives of molecularly targeted drugs in metastatic GAC

As the global trial infrastructure with regard to GAC strengthened, increasing contributions were made by Japanese and Korean investigators. In a global trial of first-line therapy, the control arm regimen should be a doublet (fluoropyrimidine plus a platinum-based drug). Many global trials recently performed included a molecularly targeted drug (Table 1). The multicenter phase III ToGA trial compared the efficacy of capecitabine plus cisplatin with and without trastuzumab. This was a large study involving 24 countries and 3665 metastatic GAC patients. The tumor samples of 810 (22 %) of these patients tested positive for *HER2* overexpression/amplification [20]. The addition of trastuzumab modestly increased the response rate and the median overall survival (13.8 months vs 11.1 months; $P = 0.0046$), and these differences reduced considerably when the results were reanalyzed after longer follow up by the US Food and Drug Administration (13.1 months vs 11.7 months). Conversely, the LOGIC trial showed no benefit of adding lapatinib to capecitabine and oxaliplatin as the first-line therapy in patients with *HER2*-amplified GAC [50]. Similarly, addition of bevacizumab (a monoclonal antibody that targets vascular endothelial growth factor) conferred no survival benefit in the AVAGAST study [51]. Addition of an EGFR-targeted drug also showed no survival benefit. The EXPAND trial reported no benefit of adding cetuximab to capecitabine plus cisplatin as first-line chemotherapy [52]. Addition of panitumumab to epirubicin, oxaliplatin, and capecitabine therapy also failed in the phase III REAL3 study [53]. The METGastric study evaluated the addition of onartuzumab (a MET/hepatocyte growth factor pathway inhibitor) to Leucovorin, 5-FU and Oxaliplatin as first-line therapy in MET-positive patients, and reported an ineffective result [54]. The phase III RILOMET-1 trials compared epirubicin, cisplatin, and capecitabine with and without rilotumumab as first-line therapy in MET-positive GAC; however, the trials were terminated following a preplanned safety review by the Data Monitoring Committee [55]. In summary, the recommended first-line therapy for metastatic GAC is trastuzumab combined with chemotherapy for HER2-positive tumor patients. Other molecularly targeted drugs, such as vascular endothelial growth factor, EGFR, and MET inhibitor, are not recommended.

As a second-line therapy, ramucirumab (an anti-vascular endothelial growth factor receptor 2 monoclonal antibody) is the only molecularly targeted drug with a confirmed minimal survival benefit in a global phase III trial [56]. In the phase III RAINBOW study, ramucirumab combined with paclitaxel yielded a higher median survival than paclitaxel alone (median 9.6 months in the ramucirumab plus paclitaxel group vs 7.4 months in the placebo plus paclitaxel group) [57]. Thus, ramucirumab plus paclitaxel is the preferred regimen in the second-line setting, and ramucirumab alone should be avoided when possible because of its limited efficacy. Other second-line therapies proved unsatisfactory. For example, the TyTAN study of Asian patients with HER2-positive GAC showed no survival benefit of lapatinib plus paclitaxel over paclitaxel alone [58]. The GRANITE-1 study, which evaluated the overall survival benefit of everolimus, showed no advantage over a placebo [59]. The phase II/III GATSBY study reported that the antibody–drug conjugate T-DM1, comprising trastuzumab linked to the cytotoxic agent emtansine, conferred no survival benefit over a taxane [60].

Promising molecularly targeted drugs against metastatic GAC

Fibroblast growth factor receptor 2 inhibitors

FGFR2 amplification especially features in the chromosomal instability and MSS/*TP53* GAC subtypes and is associated with a poor prognosis [61, 62]. Thus, fibroblast growth factor receptor 2 (FGFR2) inhibitors are considered to be potentially effective targets against GAC. Unfortunately, the SHINE study, which compared the FGFR2 inhibitor AZD4547 and paclitaxel in advanced GAC, showed that the overall median progression-free survival was similar between the AZD4547 arm and the paclitaxel arm (1.8 months vs 3.5 months) [63]. In that study, 71 of 961 patients were assigned as having *FGFR2* amplification by means of fluorescence in situ hybridization. However, FGFR2 expression was shown in only 21 % of *FGFR2*-amplified tumors. FGFR2 expression and amplification are heterogeneous. Thus, selection of FGFR2-positive patients was a problem. *FGFR2* copy number amplification in free

Table 1 Targeted therapies for gastric adenocarcinoma in global randomized clinical trials

Target	Study	Treatment	Median OS or PFS (months)	HR[a]
1st-line therapy				
HER2	ToGA [20]	XP ($n = 290$)	OS 13.8	0.74
		XP + trastuzumab ($n = 294$)	OS 11.1	(0.60–0.91)
HER2	TRIO-013/LOGiC [50]	CapeOx ($n = 238$)	OS 10.5	0.91
		CapeOx + lapatinib ($n = 249$)	OS 12.2	(0.73–1.12)
VEGF-A	AVAGAST [51]	XP ($n = 387$)	OS 10.1	0.87
		XP + bevacizumab ($n = 387$)	OS 12.1	(0.73–1.03)
EGFR	EXPAND [52]	XP ($n = 449$)	PFS 5.6	1.09
		XP + cetuximab ($n = 455$)	PFS 4.4	(0.92–1.29)
EGFR	REAL3 [53]	EOC ($n = 275$)	OS 11.3	1.37
		EOC + panitumumab ($n = 278$)	OS 8.8	(1.07–1.76)
MET	RILOMET-1 [55]	ECX ($n = 300$)	OS 11.5	1.36
		ECX + rilotumumab ($n = 300$)	OS 9.6	(1.05–1.75)
MET/HGF	METGastric [54]	mFOLFOX6	OS 11.3	0.82
		mFOLFOX6 + onartuzumab	OS 11.0	(1.05–1.75)
2nd-line therapy				
HER2	TyTAN [58]	Paclitaxel ($n = 105$)	OS 8.9	0.84
		Paclitaxel + lapatinib ($n = 98$)	OS 11.0	(0.64–1.11)
VEGFR-2	REGARD [56]	Placebo ($n = 238$)	OS 5.2	0.77
		ramucirumab ($n = 117$)	OS 3.8	(0.60–0.99)
VEGFR-2	RAINBOW [57]	Paclitaxel ($n = 335$)	OS 7.4	0.80
		Paclitaxel + ramucirumab ($n = 330$)	OS 9.6	(0.68–0.96)
mTOR	GRANITE-1 [59]	Placebo ($n = 217$)	OS 4.3	0.90
		Everolimus ($n = 439$)	OS 5.3	(0.75–1.08)

CapeOx capecitabine and oxaliplatin, *EGFR* epidermal growth factor receptor, *ECX* epirubicin, cisplatin, and capecitabine, *EOC* epirubicin, oxaliplatin, and capecitabine, *HER2* human epidermal growth factor 2, *HGF* hepatocyte growth factor, *HR* hazard ratio, *mFOLFOX6* leucovorin, fluorouracil and oxaliplatin, *mTOR* mechanistic target of rapamycin, *OS* overall survival, *PFS* progression-free survival, *VEGF-A* vascular endothelial growth factor A, *VEGFR-2* vascular endothelial growth factor receptor 2, *XP* capecitabine and cisplatin

[a] The 95 % confidence interval is given in *parentheses*.

plasma DNA was detected by digital droplet PCR in all responders to AZD4547, but not in all nonresponders [64]. Thus, free plasma DNA might have potential as a screening tool, and progress is expected in this direction.

BET-bromodomain inhibitors

Epigenetic proteins influence gene expression by modifying the DNA or histones and facilitating the packaging of DNA into chromatin; thus, they are promising cancer therapeutics [65]. Bromodomain-containing protein 4 (BRD4), which belongs to the bromodomain and extra terminal (BET) protein family, can recruit the positive transcription elongation factor complex (P-TEFb) to mitotic chromosomes and regulate *MYC*-related transcription, increasing the expression of growth-promoting genes [66, 67]. JQ1, a BRD4 inhibitor discovered in 2010 [68, 69], is a promising target against leukemia and breast cancer [70–72]. Importantly, BET inhibitors also effectively target GAC lines [73]. Therefore, clinical trials of these inhibitors have been conduced not only in advanced hematological malignancies but also in solid tumors (NCT01987362, NCT02369029, NCT02431260). The results of these and subsequent trials in GAC are expected soon.

Immune therapy

As an emerging therapy, immune checkpoint blockade has received much attention in recent years (Table 2). Two important proteins that inhibit the response of T cells to tumor cells are cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed death protein 1 (PD-1), together with its ligand (PD-L1). The first CTLA4 blocked therapy was the administration of ipilimumab to melanoma patients [74, 75]. Ipilimumab has since been administered to GAC patients, and the results of a phase II trial were

Table 2 Clinical trials of immune checkpoint blockade therapy in gastric adenocarcinoma

Study	Drug	Taget	Study phase	Line	Treatment
NCT01585987	Ipilimumab	CTLA4	II	2nd	Ipilimumab
					Best supportive care
CheckMate-032 (NCT01928394)	Nivolumab	PD-1	I/II	–	Nivolumab
	Ipilimumab	CTLA4			Nivolumab + ipilimumab
NCT02267343	Nivolumab	PD-1	III	3rd	Nivolumab
					Best supportive care
NCT02746796	Nivolumab	PD-1	II	1st	Nivolumab + SOX or CapeOX
					SOX or CapeOX
KEYNOTE-059 (NCT02335411)	Pembrolizumab	PD-1	II	–	Pembrolizumab + CS
KEYNOTE-062 (NCT02494583)	Pembrolizumab	PD-1	III	1st	Pembrolizumab
					Pembrolizumab + CS
KEYNOTE-061 (NCT02370498)	Pembrolizumab	PD-1	III	2nd	Pembrolizumab
					Paclitaxel
NCT02589496	Pembrolizumab	PD-1	II	1st	Pembrolizumab
KEYNOTE-012 (NCT01848834)	Pembrolizumab	PD-1	I	–	Pembrolizumab
NCT02340975	Tremelimumab	CTLA4	Ib/II	2nd/3rd	Tremelimumab
	Durvalumab	PD-L1			Durvalumab
					Tremelimumab + durvalumab
NCT02678182	Durvalumab	PD-L1	II	1st	Durvalumab
					Durvalumab + CS ± trastuzumab
JAVELIN Solid Tumor (NCT01772004)	Avelumab	PD-L1	Ib	2nd	Avelumab
JAVELIN Gastric 100 (NCT02625610)	Avelumab	PD-L1	III	1st	Avelumab
					FOLFOX
JAVELIN Gastric 300 (NCT02625623)	Avelumab	PD-L1	III	3rd	Avelumab
					Irinotecan or paclitaxel

CapeOx capecitabine and oxaliplatin, *CS* chemotherapy, *CTLA4* cytotoxic T-lymphocyte-associated protein 4, *FOLFOX* leucovorin, 5-fluorouracil, and oxaliplatin, *PD-1* programmed death protein 1, *PD-L1* programmed death protein 1 ligand1, *SOX* tegafur–dimeracil–oteracil potassium and oxaliplatin

recently reported [76]. After undergoing first-line chemotherapy, patients were randomized into two arms: patients who received ipilimumab or patients who received best supportive care. The immune-related progression-free survival did not differ between the two groups (hazard ratio 1.44, 80 % confidence interval 1.09–1.91, $P = 0.097$]. In 2014, the Food and Drug Administration approved the use of pembrolizumab [77, 78] and nivolumab [79] for melanoma patients. Two phase III trials have already demonstrated the efficacy of nivolumab in lung cancer [80, 81]. Moreover, in the KEYNOTE-012 study, 8 of 36 patients (22 %) with PD-L1-positive metastatic GAC responded well to pembrolizumab; further phase II and phase III trials are anticipated [82]. The phase I/II CheckMate-032 study evaluated the efficacy of combined nivolumab and ipilimumab in advanced GAC. Trials of PD-L1 are also ongoing. The phase Ib JAVELIN study on solid tumors, which is evaluating the efficacy of anti-PD-L1 antibodies as a first-line maintenance or second-line therapy, reported recently [83]. The rate of grade 3 or higher treatment-related adverse events caused by avelumab was 9.9 % and the disease control rates (median progression-free survival) in the second-line therapy and first-line maintenance groups were 29.0 % (6.0 weeks) and 57.3 % (12.0 weeks) respectively. Single-agent avelumab was sufficiently safe for administration in two randomized phase III trials in GAC. In PD-L1-positive GAC, the progression-free survival was extended in patients receiving avelumab [84]. Importantly, PD-L1 expression is a useful predictive marker in lung cancer, as tumors expressing PD-L1 are more sensitive than other tumor types [80, 81]. The KEYNOTE-012 study highlighted interferon-γ gene expression as a potentially predictive marker of pembrolizumab response in the PD-L1-positive population [82].

A novel immunotherapy agent, IMAB362, was recently reported. IMAB362 is a chimeric monoclonal antibody that causes death of cancer cells with expression of isoform 2 of the tight junction molecule claudin 18 (CLDN18.2) by activation of immune effector mechanisms. CLDN18.2 is important for cell adhesion, integrity, and other tissue-

specific functions and is highly expressed in gastric cancer [85, 86]. The phase II FAST trial evaluated the addition of IMAB362 to chemotherapy for patients with CLDN18.2-positive advanced gastric cancers, showing that the median overall survival was 8.4 months for the chemotherapy-alone group versus 13.2 months for the IMAB362 group [87]. The results of these studies have led to pivotal trials in GAC being planned and which are expected soon.

Summary

Until recently, treatment strategies for metastatic GAC differed in different regions. However, globalization has resulted in acceptance of a reference regimen containing a platinum compound and a fluoropyrimidine. Given the high burden of GAC in East Asia, the opportunity is ripe for Japanese, Korean, and Chinese investigators from Asia to contribute more to GAC research. Moving forward, empiric approaches with little or no success need to be replaced with more rigorous and rational approaches.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This article does not contain any studies with human or animal subjects performed by any of the authors.

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