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REVIEW ARTICLE

Second-line chemotherapy for patients with advanced gastric cancer

Daisuke Takahari[1]

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Abstract The first choice for treating patients with metastatic gastric cancer is chemotherapy, and combination therapy with fluorouracil, platinum, and trastuzumab has been established as the standard first-line chemotherapy. For further improvement of treatment outcomes, it is important to develop second- and third-line chemotherapy. In the first decade of this century, irinotecan and taxanes, cytotoxic agents, and various molecular targeted agents began to be developed as second-line therapy. Treatment with paclitaxcel weekly in combination with ramucirumab targeting vascular endothelial growth factor receptor 2 has become the first choice for second-line therapy. Immune checkpoint inhibitors are now being developed, and the current treatment strategies for advanced gastric cancer may undergo major changes in the future. This review summarizes the transitions and future prospects of clinical developments for second-line therapy in patients with advanced gastric cancer.

Keywords Gastric cancer · Paclitaxel · Irinotecan · Ramucirumab · Chemotherapy

Introduction

According to Torre at al. [1] gastric cancer was the fourth most frequently diagnosed cancer and the third leading cause of cancer-related death worldwide in 2012, with 951,600 new cases and 723,100 deaths globally. The prevalence of gastric cancer, though high on a global basis, is highest in East Asia. Treatment options for gastric cancer, such as surgery, chemotherapy, and radiotherapy, differ depending on the tumor status. Chemotherapy is the first choice for the treatment of patients with metastatic gastric cancer. In these patients, the main objectives of chemotherapy are survival prolongation, symptom palliation, and quality-of-life improvement. In the 1990s, prospective clinical trials and meta-analyses demonstrated the survival benefits of chemotherapy as compared with best supportive care (BSC) [2–5]. Clinical developments for first-line treatment of advanced gastric cancer (AGC) began to be increasingly actively developed in Asia, Europe, and the USA to enhance their clinical benefits. As a result, combination therapy with 5-fluorouracil (5-FU) plus platinum and with 5-FU plus platinum plus docetaxel/epirubicin has been established as standard treatment [6–12].

The pooled analysis data from two phase III trials (JCOG9205 and JCOG9912) of first-line chemotherapy for patients with AGC conducted by the Japan Clinical Oncology Group confirmed that patients treated in the JCOG9912 trial had a better prognosis than patients in the JCOG9205 trial. This result can be interpreted as suggesting that the improved efficacy of first-line chemotherapy with 5-FU-based therapy and second-line chemotherapy as well as subsequent-line chemotherapy with new agents, such as irinotecan, docetaxel, and paclitaxel, contributed significantly to the improved survival [13]. In a phase III trial (SPIRITS) of first-line chemotherapy conducted to verify the superiority of S-1 and cisplatin (SP) over S-1, median overall survival (OS) was 13.0 months in the SP group and 11.0 months in the S-1 group [hazard ratio (HR) 0.77; 95% confidence interval

✉ Daisuke Takahari
daisuke.takahari@jfcr.or.jp

[1] Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31, Ariake, Koto-ku, Tokyo 135-8550, Japan

(CI) 0.61–0.98; $P = 0.04$]. Seventy-five percent of the patients received second-line treatment after completion of the trial: those who received taxane (docetaxel or paclitaxel)-based posttreatment accounted for 51% of the SP group and 40% of the S-1 group, and those who received irinotecan-based posttreatment accounted for 14% and 15% respectively. From the results of these historical studies, a treatment strategy for first-line chemotherapy as well as for second- and subsequent-line chemotherapy is thought to be important for the prolongation of survival in AGC patients.

Cytotoxic agents

Data have been reported from a number of phase II and phase III trials conducted to investigate the efficacy of second-line chemotherapy with irinotecan, docetaxel, or paclitaxel in patients with AGC [14–33] (Table 1).

Irinotecan and taxanes (docetaxel, paclitaxel, nab-paclitaxel)

The Arbeitsgemeinschaft Internistische Onkologie (AIO) in Germany conducted a phase III trial to verify the superiority of irinotecan over BSC in terms of OS with the aim of proving the efficacy of second-line chemotherapy for AGC [28]. Despite its initial plan to include a total of 120 patients in both treatment groups, the trial could not enroll more than 40 patients and had to be terminated prematurely. The median OS was 4.0 months in the irinotecan group (250 mg/m^2 every 3 weeks) and 2.4 months in the BSC group (HR 0.48; 95% CI 0.25–0.92; $P = 0.012$), suggesting the superiority of treatment in the irinotecan group. This was the first clinical trial, albeit in a small number of patients, that suggested the efficacy of second-line chemotherapy for AGC.

In Korea, a phase III trial was conducted to verify the superiority of docetaxel or irinotecan over BSC in terms of OS in second-line chemotherapy for AGC [29]. Patients were randomized into either a salvage chemotherapy (SLC) group or a BSC group at a ratio of 2:1 (133 patients in the SLC group and 69 patients in the BSC group). Those in the SLC group received either of the following treatments at the discretion of the investigator: docetaxel at 60 mg/m^2 every 3 weeks or irinotecan at 150 mg/m^2 every 2 weeks. The median OS was 5.3 months in the SLC group and 3.8 months in the BSC group, showing that survival in the SLC group was significantly prolonged (HR 0.657; 95% CI 0485–0.891; $P = 0.007$). There was no statistically significant difference in OS between the docetaxel cohort (5.2 months) and the irinotecan cohort (6.5 months) ($P = 0.116$). The incidence of adverse events was similar in both the docetaxel cohort and the irinotecan cohort (neutropenia, 15% vs 18%; anemia, 30% vs 32%). This was the first large-scale phase III trial that verified the efficacy of second-line chemotherapy in patients with AGC.

Another phase III trial, COUGAR-02, was conducted in patients with esophagogastric adenocarcinoma to compare docetaxel and active symptom control [30]. This was also the first phase III trial of second-line chemotherapy that evaluated health-related quality of life in patients previously treated with 5-FU and platinum. One hundred sixty-eight patients (84 for each group) were enrolled in the United Kingdom. The OS was 5.2 months in the docetaxel group (75 mg/m^2 every 3 weeks; treatment was continued for up to 6 cycles), which was significantly longer than the 3.6 months in the active symptom control group (HR 0.67; 95% CI 0.49–0.92; $P = 0.01$). In the evaluation based on the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30), although there was no significant difference in functional scales or overall quality of life between the two groups, assessments of some of the symptom subscales showed significantly better results in the docetaxel group compared with the active symptom control group (pain, $P = 0.0008$; abdominal pain, $P = 0.01$; nausea and vomiting, $P = 0.02$; and constipation, $P = 0.02$).

Paclitaxel is an established standard treatment for a wide variety of cancer types. For the treatment of AGC, paclitaxel was developed as an agent administered in a every 3 weeks regimen. Although it also shows a modest overall response rate (ORR) (26–27%) as second-line chemotherapy, paclitaxel is known to cause hematotoxicity, in particular, a high incidence (37–88%) of grade 3 or greater neutropenia [17, 18]. In Japan, a weekly regimen of paclitaxel was actively developed to reduce hematotoxicity [19–21, 23, 24]. Because its efficacy is comparable to the every 3 weeks regimen while causing fewer severe adverse events, the weekly regimen of paclitaxel has come to be widely used in clinical practice in Japan.

WJOG4007, a phase III trial that enrolled 223 patients in Japan, was conducted to verify the superiority of irinotecan over a weekly regimen of paclitaxel [31]. The OS was 8.4 months in the irinotecan group (150 mg/m^2 on days 1 and 15, every 4 weeks) and 9.5 months in the group that received paclitaxel weekly (80 mg/m^2 on days 1, 8, and 15, every 4 weeks), failing to demonstrate the superiority of irinotecan over a weekly regimen of paclitaxel (HR 1.13; 95% CI 0.86–1.49; $P = 0.38$). Progression-free survival (PFS) was 2.3 months in the irinotecan group and 3.6 months in the group that received paclitaxel weekly (HR 1.14; 95% CI 0.88–1.49; $P = 0.33$). The following grade 3 or higher adverse events were reported in the group that received paclitaxel weekly and the irinotecan group:

Table 1 Clinical trials of second-line chemotherapy for patients with advanced gastric cancer—a summary of major trials

Trial name/authors	Phase	Regimens	No. of patients	Median OS	HR, *P*	Median PFS	HR, *P*
Graziano et al. [14]	II	Docetaxel (36 mg/m^2) q1w	21	3.5 months	NA	NR	NA
Assersohn et al. [15]	II	5-FU (400 mg/m^2)/leucovorin (125 mg/m^2) + irinotecan (180 mg/m^2) followed by 5-FU (1200 mg/m^2) q2w	38	6.4 months	NA	3.7 months (FFS)	NA
Giuliani et al. [16]	II	Irinotecan (150 mg/m^2) + mitomycin C (8 mg/m^2), day 1; irinotecan (150 mg/m^2), day 15	38	8 months	NA	NR	NA
Yamada et al. [17]	II	Paclitaxcel (210 mg/m^2) q3w	60	340 days	NA	NR	NA
Yamaguchi et al. [18]	II	Paclitaxcel (210 mg/m^2) q3w	32	234 days	NA	NR	NA
CCOG0302 study, Kodera et al. [19]	II	Paclitaxcel (80 mg/m^2) q1w	44	7.8 months	NA	2.6 months	NA
Matsuda et al. [20]	II	Paclitaxcel (80 mg/m^2) q1w	33	8 months	NA	5.6 months (TTP)	NA
Im et al. [21]	II	Paclitaxcel (70 mg/m^2) q1w	52	5.1 months	NA	3.5 months	NA
JCOG0109-DI trial, Hamaguchi et al. [22]	II	Irinotecan (150 mg/m^2) + mitomycin C (5 mg/m^2) q2w	45	10.1 months	NA	4.1 months	NA
Shitara et al. [23]	Randomized	Paclitaxcel (80 mg/m^2, day 1; 100 mg/m^2, day 8; 120 mg/m^2, day 15) q1w	45	11.8 months	HR 0.75, $P = 0.12$	4.3 months	HR 0.55, $P = 0.017$
	Phase II	Paclitaxcel (80 mg/m^2) q1w	44	9.6 months		2.5 months	
JCOG0407	II	Paclitaxcel (80 mg/m^2) q1w	51	7.7 months	HR 0.89, $P = 0.298$	3.7 months	HR 0.58, $P = 0.005$
Nishina et al. [24]		5-FU (800 mg/m^2, days 1–5) or 5-FU (600 mg/m^2, day 1) + leucovorin (10 mg/m^2, days 2–3) + methotrexate (100 mg/m^2, day 1)	48	7.7 months		2.4 months	
TCOG GI-0801/ BIRIP trial, Higuchi et al. [25]	III	Irinotecan (60 mg/m^2) + cisplatin (30 mg/m^2) q2w	64	10.7 months	HR 1.00, $P = 0.9823$	3.8 months	HR 0.68, $P = 0.0398$
		Irinotecan (150 mg/m^2) q2w	63	10.1 months		2.8 months	
TRICS trial, Nishikawa et al. [26]	III	Irinotecan (60 mg/m^2) + cisplatin (30 mg/m^2) q2w	84	13.9 months	HR 0.834, $P = 0.288$	4.6 months	HR 0.860, $P = 0.376$
		Irinotecan (150 mg/m^2) q2w	84	12.7 months		4.1 months	
JACCRO GC-05, Tanabe et al. [27]	II/III	S-1 (80 mg/m^2, days 1–14) + irinotecan (150 mg/m^2 q3w)	145	8.8 months	HR 0.99, $P = 0.92$	3.8 months	HR 0.85, $P = 0.16$
		Irinotecan (150 mg/m^2) q2w	148	9.5 months		3.4 months	
Thuss-Patience et al. [28]	III	Irinotecan (250–350 mg/m^2) q3w	21	4.0 months	HR 0.48, $P = 0.012$	2.5 months	NA
		BSC	19	2.4 months		NA	
Kang et al. [29]	III	Salvage chemotherapy (docetaxel 60 mg/m^2 q3w or irinotecan 150 mg/m^2 q2w)	133	5.3 months	HR 0.657, $P = 0.007$	NA	NA
		BSC	69	3.8 months			

Table 1 continued

Trial name/authors	Phase	Regimens	No. of patients	Median OS	HR, *P*	Median PFS	HR, *P*
COUGAR-02, Ford et al. [30]	III	Docetaxel (75 mg/m^2) q3w	84	5.2 months	HR 0.67, $P = 0.01$	12.2 weeks (TTP)	NA
		Active symptom control	84	3.6 months		NA	
WJOG4007, Hironaka et al. [31]	III	Irinotecan (150 mg/m^2) q2w	108	8.4 months	HR 1.13, $P = 0.38$	2.3 months	HR 1.14, $P = 0.33$
		Paclitaxel (80 mg/m^2) q1w	111	9.5 months		3.6 months	
Sasaki et al. [32]	II	Nab-paclitaxel (260 mg/m^2) q3w	56	9.2 months	NA	2.9 months	NA
ABSOLUTE, Shitara et al. [33]	III	Nab-paclitaxel (100 mg/m^2) q1w	240	11.1 months	HR 0.97, $P = 0.0085$ (nab-paclitaxel q1w vs paclitaxel q1w)	5.3 months	HR 0.88 (nab-paclitaxel q1w vs paclitaxel q1w)
		Nab-paclitaxel (260 mg/m^2) q3w	243	10.3 months		3.8 months	
		Paclitaxel (80 mg/m^2) q1w	243	10.9 months	HR 1.06, $P = 0.062$ (nab-paclitaxel q3w vs paclitaxel q1w)	3.8 months	HR = 1.03 (nab-paclitaxel q3w vs paclitaxel q1w)

BSC best supportive care, *FFS* failure-free survival, *5-FU* 5-fluorouracil, *HR* hazard ratio, *NA* not applicable, *NR* not reached, *OS* overall survival, *PFS* progression-free survival, *TTP* time to treatment failure, *q1w* every week, *q2w* every 2 weeks, *q3w* every 3 weeks

leukopenia (20.4% and 19.1% respectively), neutropenia (28.7% and 39.1% respectively), hemoglobin (21.3% and 30.0% respectively), peripheral sensory neuropathy (7.4% and 0% respectively), and febrile neutropenia (2.8% and 9.1% respectively). Compared with the results of the two previously mentioned phase III trials (the AIO trial and the Korean trial) [28, 29], the OS tended to be longer in both the group that received paclitaxel weekly and the irinotecan group. These results were considered to reflect the following facts: (1) patients assessed as having performance status 0 or 1 accounted for about 96%; (2) about half of the patients had a single metastatic site; and (3) the proportion of patients with severe peritoneal metastasis was lower than that previously reported data (AIO trial, 43%; Korean trial, 45%; WJOG4007 trial, 25.6%). On the basis of the results of the WJOG4007 trial, weekly paclitaxel has become preferentially selected over irinotecan as second-line chemotherapy for AGC.

Nab-paclitaxel, a 130-nm, albumin-bound nanoparticle formulation of paclitaxel, does not contain Cremophor® EL or anhydrous ethanol, solvents present in conventional paclitaxel formulations, and does not require patients to receive prior treatment for the prevention of hypersensitivity. In Japan, a phase II trial of nab-paclitaxel given every 3 weeks (260 mg/m^2 every 3 weeks) was conducted as second-line chemotherapy for patients with AGC. The ORR was 27.8%, the median PFS was 2.9 months (95% CI 2.4–3.6 months), and the median OS was 9.2 months (95% CI 6.9–11.4 months) [32]. On the basis of the results of this phase II trial, nab-paclitaxel given every 3 weeks was approved in Japan for the indication of AGC in February 2013. However, because paclitaxel used globally was given as a weekly regimen, development of nab-paclitaxel as a weekly regimen was highly demanded. Given this situation, ABSOLUTE, a phase III trial that enrolled 741 patients in Japan, was conducted [33]. The OS was 11.1 months in the group that received nab-paclitaxel every week (100 mg/m^2; days 1, 8, and 15; every 4 weeks) and 10.9 months in the control group, which received paclitaxel every week (HR 0.97; 95% CI 0.76–1.23; $P = 0.0085$), demonstrating the noninferiority of weekly nab-paclitaxel in comparison with weekly paclitaxel. Meanwhile, the OS in the group that received nab-paclitaxel every 3 weeks was 10.3 months (HR 1.06; 95% CI 0.87–1.31; $P = 0.062$), failing to demonstrate noninferiority with respect to weekly paclitaxel. Although the common adverse events reported in the group that received nab-paclitaxel weekly were hematologic events, such as neutropenia, similar to those reported in the group that received paclitaxel weekly, the incidence of peripheral sensory neuropathy in the group that received nab-paclitaxel weekly was comparable to that in the group that received paclitaxel weekly, and anaphylaxis, an event of

Table 2 Clinical trials of second-line targeted therapy for patients with advanced gastric cancer—a summary of major trials

Trial name/authors	Phase	Target	Regimens	No. of patients	Median OS	HR, *P*	Median PFS	HR, *P*
JFMC45-1102, Nishikawa et al. [35]	II	HER2	Paclitaxel (80 mg/m^2) q1w + trastuzumab (8 mg/kg) q3w	47	17.1 months	NA	5.1 months	NA
TyTAN, Satoh et al. [37]	III	HER2	Paclitaxel (80 mg/m^2) q1w + lapatinib (1500 mg/day)	132	11.0 months	HR 0.84, $P = 0.1044$	5.4 months	HR 0.85, $P = 0.2441$
			Paclitaxel (80 mg/m^2) q1w	129	8.9 months		4.4 months	
GATSBY, Kang et al. [38]	II/III	HER2	T-DM1 (2.4 mg/kg) q1w	228	7.9 months	HR 1.15, $P = 0.8589$	2.7 months	HR 1.13, $P = 0.3080$
			Paclitaxel (80 mg/m^2) q1w or docetaxcel (75 mg/m^2) q3w	117	8.6 months		2.9 months	
REGARD, Fuchs et al. [40]	III	VEGFR2	Ramucirumab (8 mg/kg) q2w	238	5.2 months	HR 0.776, $P = 0.047$	2.1 months	HR 0.483, $P < 0.0001$
			Placebo	117	3.8 months		1.3 months	
RAINBOW, Wilke et al. [41]	III	VEGFR2	Paclitaxel (80 mg/m^2) q1w + ramucirumab (8 mg/kg) q2w	330	9.6 months	HR 0.807, $P = 0.017$	4.4 months	HR 0.635, $P < 0.0001$
			Paclitaxel (80 mg/m^2) q1w + placebo	335	7.4 months		2.9 months	
RAINBOW, Japanese population, Shitara et al. [42]	III	VEGFR2	Paclitaxel (80 mg/m^2) q1w + ramucirumab (8 mg/kg) q2w	68	11.4 months	HR 0.880, $P = 0.5113$	5.6 months	HR 0.503, $P = 0.0002$
			Paclitaxel (80 mg/m^2) q1w + placebo	72	11.5 months		2.8 months	
GRANITE-1,[a] Ohtsu et al. [46]	III	mTOR	Everolimus (10 mg/day) + BSC	439	5.4 months	HR 0.90, $P = 0.124$	1.7 months	HR 0.66, $P < 0.001$
			Placebo + BSC	217	4.3 months		1.4 months	
Bang et al. [50]	II	PARP	Paclitaxel (80 mg/m^2) q1w + olaparib (100 mg/day)	62	13.10 months	HR 0.56, $P = 0.005$	3.91 months	HR 0.80, $P = 0.131$
				62	8.30 months		3.55 months	
			Paclitaxel (80 mg/m^2) q1w + placebo	ATM_{low}	ATM_{low}	HR 0.35, $P = 0.002$	ATM_{low}	HR 0.74, $P = 0.157$
				31	NR		5.29 months	
				32	8.20 months		3.68 months	
GOLD, Bang et al. [51]	III	PARP	Paclitaxel (80 mg/m^2) q1w + olaparib (200 mg/day)	263	8.8 months	HR 0.79,[b] $P = 0.0262$	3.91 months	HR 0.80, $P = 0.131$
				262	6.9 months		3.55 months	
			Paclitaxel (80 mg/m^2) q1w + placebo	ATM_{low}	ATM_{low}	HR 0.73, $P = 0.2458$	ATM_{low}	HR 0.74, $P = 0.157$
				48	12.0 months		5.29 months	
				46	10.0 months		3.68 months	
Satoh et al. [54]	II	EGFR	Irinotecan (150 mg/m^2) q2w + nimotuzumab (400 mg) q1w	38	250.5 days	HR 0.994, $P = 0.9778$	85.0 days	HR 0.860, $P = 0.5668$
				39	232.0 days		73.0 days	
			Irinotecan (150 mg/m^2) q2w	6	EGFR 2+/3+	HR 0.369, $P = 0.0944$	EGFR 2+/3+	HR 0.341, $P = 0.1293$
					358.5 days		118.5 days	
				8	229.5 days		59.0 days	

ATM_{low} low level of ataxia telangiectasia mutated, *BSC* best supportive care, *EGFR* epidermal growth factor receptor, *HER2* human epidermal growth factor receptor 2, *HR* hazard ratio, *mTOR* mammalian target of rapamycin, *NA* not applicable, *NR* not reached, *OS* overall survival, *PARP* poly(ADP-ribose) polymerase, *PFS* progression-free survival, *q1w* every week, *q2w* every 2 weeks, *q3w* every 3 weeks, *VEGFR2* vascular endothelial growth factor receptor 2,

[a] This trial targeted second-line and third-line advanced gastric cancer patients.

[b] Because of the Hochberg multiple testing procedure, the statistical significance was less than 0.025 for each population.

concern in the group that received paclitaxcel weekly (2%), did not occur in any patients in the group that received nab-paclitaxcel weekly. If weekly nab-paclitaxcel were to be approved in Japan, it would become a treatment option as second-line chemotherapy for AGC.

Molecular targeted therapies

For the treatment of AGC, molecular targeted agents started to be developed in the first decade of this century, targeting various molecules. At present, trastuzumab, an anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody, and ramucirumab, an anti-vascular endothelial growth factor receptor 2 monoclonal antibody, are the only molecular targeted agents that have been successfully developed and are currently available on the market (Table 2). Several types of molecular targeted agents are currently being developed, and are expected to serve as future treatment options (Table 3).

Anti-HER2 antibody

Treatment with trastuzumab, an anti-HER2 monoclonal antibody, was established as a standard first-line therapy for AGC after its efficacy as first-line chemotherapy had been verified in HER2-positive patients [34]. No phase III trials have been conducted to investigate the efficacy and safety of trastuzumab as second-line therapy. In a phase II trial in HER2-positive patients with AGC who had previously been treated with chemotherapy other than trastuzumab therapy, the efficacy and safety of a combination of paclitaxcel given weekly and trastuzumab (8 mg/kg; every 3 weeks) were observed [35]. The ORR was 37% (95% CI 23–52%) and the PFS and OS were 5.1 months (95% CI 3.8–6.5 months) and 17.1 months (95% CI 13.5–18.6 months) respectively. The grade 3 or higher adverse events reported in the trial were neutropenia (32.6%), leukopenia (17.4%), anemia (15.2%), and hypoalbuminemia (8.7%).

Lapatinib is a molecular targeted agent that targets HER2, similarly to trastuzumab, and also epidermal growth factor receptor (EGFR), unlike trastuzumab. The add-on effect of lapatinib with regard to capecitabine was verified in a phase III trial in patients with advanced breast cancer who had previously been treated with an anthracycline, a taxane, and trastuzumab [36]. The add-on effect of lapatinib with regard to paclitaxcel given weekly was evaluated in a phase III trial of second-line chemotherapy in HER2-positive patients with AGC [37]. Two hundred sixty-one patients were randomized into either a group that received lapatinib plus paclitaxcel weekly ($n = 132$) or a group that receivved paclitaxcel weekly ($n = 129$). The median OS was 11.0 months in the group that lapatinib plus paclitaxcel weekly and 8.9 months in the group that received paclitaxcel weekly (HR 0.84; 95% CI 0.64–1.11; $P = 0.1044$). In a subgroup analysis of OS by immunohistochemistry (IHC) status, lapatinib showed a tendency of an add-on effect among patients with IHC status 3+. The results of this trial may have been affected by the fact that the percentage of enrolled patients with IHC stats 0 or 1+ was as high as 35%. It will be necessary to obtain data from a confirmatory trial in patients with IHC status 3+ only.

Table 3 Ongoing trials for second-line patients in advanced gastric cancer—a summary of major trials

Regimens	Trial name/clinical trial registration	Phase	Target	No. of patients	Locations
Ramucirumab + nab-paclitaxel q1w	JapicCTI-153088	II	VEGFR2	40	Japan
Ramucirumab + nab-paclitaxel q1w	NCT02317991	II	VEGFR2	65	USA
Nimotuzumab + irinotecan	ENRICH NCT01813253	III	EGFR	400	Asia
BBI-608 + paclitaxel q1w	BRIGHTER NCT02178956	III	STAT3	700	Global
Pembrolizumab	KEYNOTE-061 NCT02370498	III	PD-1	720	Global
Nivolumab + oxaliplatin + S-1 or capecitabine	NCT02746796	II	PD-1	268	Japan, Korea
Nivolumab	NCT02267343	III	PD-1	480	Japan, Korea, Taiwan

EGFR epidermal growth factor receptor, *PD-1* programmed cell death 1, *q1w* every week, *STAT3* signal transducer and activator of transcription 3, *VEGFR2* vascular endothelial growth factor receptor 2

Ado-trastuzumab emtansine (T-DM1), the other novel anti-HER2 monoclonal antibody, is a molecular targeted agent consisting of trastuzumab linked to emtansine (DM1), a microtubule inhibitor. The efficacy and safety of second-line chemotherapy with T-DM1 were compared with those of a taxane in HER2-positive patients with AGC or advanced esophagogastric junction (EGJ) cancer in a phase II/III trial [38]. On the basis of advice given by the independent data monitoring committee after completion of the phase II part of the trial, the recommended dose of T-DM1 for the phase III part of the trial was determined to be 2.4 mg/kg, administered once weekly. Three hundred forty-five patients were randomized into either a group that received T-DM1 at 2.4 mg/kg ($n = 228$) or a taxane group ($n = 117$) in 28 countries. The taxane group consisted of 69 patients in the cohort hat received docetaxel every 3 weeks and 42 patients in cohort that received paclitaxcel every week. The median OS was 7.9 months in the T-DM1 group and 8.6 months in the taxane group (HR 1.15; 95% CI 0.87–1.51; $P = 0.8589$), failing to show any superior clinical benefits of T-DM1 over taxane, a standard treatment, in terms of efficacy. On the basis of the results of this trial, the development of T-DM1 for the treatment of gastric cancer was discontinued.

Anti-VEGF antibody

Bevacizumab, a molecular targeted agent binding specifically to vascular endothelial growth factor (VEGF), has demonstrated its efficacy against colorectal cancer, non-small-cell lung cancer, breast cancer, ovarian cancer, cervical cancer, and malignant glioma. The agent is also being tested for the treatment of gastric cancer. A phase III trial (AVAGAST) of first-line chemotherapy for patients with AGC or advanced EGJ cancer was conducted to investigate the add-on effect of bevacizumab with regard to capecitabine plus cisplatin (XP) or 5-FU plus cisplatin (FP) [39]. The median OS was 12.1 months in the XP/FP plus bevacizumab group and 10.1 months in the XP/FP plus placebo group (HR 0.87; 95% CI 0.73–1.03; $P = 0.1002$), showing no significant prolongation of OS when bevacizumab was added to the therapy. Of the enrolled patients in the respective regions, the following percentages of patients received second-line chemotherapy: 66% in the Asia-Pacific region (OS 12.1 months), 31% in the European region (OS 8.6 months), and 21% in the pan-American region (OS 6.8 months). These OS data by region suggest the possibility of second-line chemotherapy being a factor for the prolongation of survival.

Ramucirumab is a recombinant human monoclonal immunoglobulin G1 antibody against human VEGF receptor 2 (VEGFR2), which plays an important role in angiogenesis involved in cancer growth and metastases. Ramucirumab binds specifically to the extracellular domain of VEGFR2 and inhibits the interaction of VEGFR2 with its ligands (not only VEGF-A, but also VEGF-C, and VEGF-D), and thereby inhibits signaling and angiogenesis of cancer, exerting an antitumor effect. Two phase III trials (REGARD and RAINBOW) of second-line therapy for patients with AGC were conducted [40, 41]. In the REGARD trial, the efficacy and safety of second-line therapy with ramucirumab were evaluated in patients with AGC or advanced EGJ cancer who had received first-line chemotherapy [40]. Three hundred fifty-five patients (238 in the ramucirumab group and 117 in the placebo group) were enrolled in the trial in 29 countries (Japan did not participate). The median OS was 5.2 months in the ramucirumab group and 3.8 months in the placebo group (HR 0.776; 95% CI 0.603–0.998; $P = 0.047$), demonstrating the superiority of ramucirumab over placebo. The incidence of all grades adverse events was 94% in the ramucirumab group, which was similar to that in the placebo group (88%). No grade 3 or higher adverse events with an incidence of more than 10% were reported in the ramucirumab group. The incidence of hypertension, a VEGF-antibody-specific event, was 16% in the ramucirumab group, which was higher than that in the placebo group (8%). Ramucirumab was not associated with increased rates of fatigue, emesis, or other notable toxic effects. Ramucirumab, anti-VEGFR2 antibody, is the first molecular targeted agent that has demonstrated efficacy of second-line therapy in patients with AGC.

The add-on effect of ramucirumab with regard to paclitaxcel, a standard chemotherapy agent used as second-line treatment for AGC, was observed in the RAINBOW trial [41]. Six hundred sixty-five patients were enrolled in the trial in 27 countries. Of these 665 patients, 330 patients were randomized into a group that received paclitaxcel weekly plus ramucirumab and 335 patients were randomized into a group that received paclitaxcel weekly. The median follow-up time was 7.9 months. The median OS was 9.6 months in the group that received paclitaxcel weekly plus ramucirumab group and 7.4 months in the group that received paclitaxcel weekly (HR 0.807; 95% CI 0.678–0.962; $P = 0.017$), demonstrating the add-on effect of ramucirumab. The PFS was 4.4 months in the group that received paclitaxcel weekly plus ramucirumab and 2.9 months in the group that received paclitaxcel weekly (HR 0.635; 95% CI 0.536–0.752; $P < 0.0001$), demonstrating that ramucirumab had an add-on effect for PFS similar to that seen for OS. The results of subgroup analyses conducted to compare Japanese and Western patients in the RAINBOW trial were also reported [42]. In the 68 Japanese patients in the group that received paclitaxcel weekly plus ramucirumab and in the 72 Japanese patients

in the group that received paclitaxcel weekly, the median OS was 11.4 months and 11.5 months respectively (HR 0.880; $P = 0.5113$) and the median PFS was 5.6 months and 2.8 months respectively (HR 0.503; $P = 0.0002$). In the 198 Western patients in the group that received paclitaxcel weekly plus ramucirumab and the 200 Western patients in the group that received paclitaxcel weekly, the median OS was 8.6 months and 5.9 months respectively (HR 0.726; $P = 0.0050$) and the median PFS was 4.2 months and 2.8 months respectively (HR, 0.631; $P \leq 0.0001$). These results showed that the Japanese subgroup achieved an improvement in PFS, though not in OS. Ramucirumab therapy and weekly paclitaxcel therapy plus ramucirumab therapy are recommended as standard second-line chemotherapy for AGC in the National Comprehensive Cancer Network clinical practice guidelines [43], the European Society for Medical Oncology clinical practice guidelines [44], and the Japanese gastric cancer treatment guidelines [45]. Phase II trials of combination therapy with nab-paclitaxcel given weekly and ramucirumab (JapicCTI-153088, NCT02317991) are being conducted in Japan and the USA and are expected to contribute to the development of more treatment approaches.

Mammalian target of rapamycin inhibitor

Mammalian target of rapamycin, located in the downstream part of the phosphatidylinositol 3-kinase/Akt signaling pathway regulates cell proliferation and cell death. Everolimus is an orally administered mammalian target of rapamycin inhibitor, and its efficacy has been confirmed in the treatment of various types of cancer. The efficacy of everolimus as second- and third-line chemotherapy for AGC was evaluated in the GRANITE-1 trial. The median OS was 5.4 months in the everolimus group and 4.3 months in the placebo group (HR 0.90; 95% CI 0.75–1.08; $P = 0.124$), failing to show the efficacy of everolimus [46]. After completion of enrollment in the GRANITE-1 trial, the GRANITE-2 trial (NCT01248403) was started to verify the add-on effect of everolimus with regard to weekly paclitaxcel therapy. However, since the efficacy of everolimus could not be verified in the GRANITE-1 trial, the GRANITE-2 trial was also terminated and the development of everolimus for the treatment of gastric cancer was discontinued.

Poly(ADP-ribose) polymerase inhibitor

In the *BRCA1*/*BRCA2* gene involved in the homologous recombination pathway for DNA repair, loss of function associated with genetic mutation is known in breast cancer and ovarian cancer. Poly(ADP-ribose) polymerase (PARP) is involved in base excision repair, a DNA modification. Cells with the *BRCA1*/*BRCA2* gene mutation cannot repair DNA damage caused by PARP inhibition and this eventually result in cell death. Olaparib, an orally administered PARP inhibitor, acts specifically on cells with DNA repair pathway defects and induces cell death. It is the first PARP inhibitor to be approved for the indication of BRCA gene mutation positive advanced ovarian cancer in the USA and the European Union and is also effective in the treatment of BRCA-positive prostate cancer [47, 48]. Preclinical data suggested that olaparib, a PARP inhibitor, is effective for treating gastric cancer patients with a low ataxia telangiectasia mutated (ATM) protein level [49]. A study to evaluate add-on effect of olaparib with regard to weekly paclitaxcel therapy as second-line chemotherapy for patients with AGC was conducted in Korea [50]. In this study, 124 patients were treated with either paclitaxcel weekly plus olaparib or paclitaxcel weekly plus placebo. The median duration of follow-up for the overall population was 8.4 months (0.3–26.2 months). The PFS, the primary end point, was 3.91 months with olaparib versus 3.55 months with weekly paclitaxcel therapy plus placebo (HR 0.80; 80% CI 0.62–1.03; $P = 0.131$). The OS, the secondary end point, was 13.1 months with olaparib versus 8.3 months with weekly paclitaxcel therapy plus placebo (HR 0.56; 95% CI 0.35–0.87; $P = 0.010$; 80% CI 0.41–0.75; $P = 0.005$). In the low ATM expression population, the OS in the group that received paclitaxcel weekly plus olaparib was not reached because of lack of events and in the group that received paclitaxcel weekly plus placebo it was 8.2 months (HR 0.35; 80% CI 0.22–0.56; $P = 0.002$). On the basis of these results, a phase III trial (GOLD) was conducted in four Asian countries [51]. The experimental group received paclitaxcel weekly plus olaparib (100 mg tablet twice daily) and the control group received paclitaxcel weekly plus placebo. This trial used co-primary end points to evaluate the OS in all patients and ATM protein negative patients. The median OS in all patients was 8.8 months in the group that received paclitaxcel weekly plus olaparib and 6.9 months in the group that received paclitaxcel weekly plus placebo (HR 0.79; 97.5% CI 0.63–1.00; $P = 0.0262$). The OS in ATM protein-negative patients was 12.0 months in the group that received paclitaxcel weekly plus olaparib group and 10.0 months in the group that received paclitaxcel weekly plus placebo (HR 0.73; 97.5% CI 0.40–1.34; $P = 0.2458$), showing no statistically significant differences between these patient populations. Because of these results, it has become difficult to pursue the development of olaparib for the treatment of AGC.

EGFR inhibitor

To develop an anti-EGFR antibody for the treatment of AGC, two phase III trials (REAL-3 and EXPAND) were conducted. Although the REAL-3 trial was conducted to verify the add-on effect of panitumumab with regard to a combination of epirubicin, oxaliplatin, and capecitabine, and the EXPAND trial was conducted to verify the add-on effect of cetuximab with respect to XP, neither study could verify that anti-EGFR antibody agents had any add-on effects [52, 53].

Nimotuzumab is a humanized immunoglobulin G1 antibody against EGFR. The effect of a combination of irinotecan and nimotuzumab was compared with that of single-agent irinotecan as second-line chemotherapy for patients with AGC in a randomized phase II trial [54]. The PFS was 73.0 days in the irinotecan group and 85.0 days in the irinotecan plus nimotuzumab group (HR 0.860; $P = 0.5668$), and the OS was 250.5 days and 232.0 days respectively (HR 0.994; $P = 0.9778$), showing no statistically significant differences between the two groups. However, in a subgroup analysis in patients who had the highest EGFR expression (2+/3+), the PFS was 59.0 days in the irinotecan group and 118.5 days in the irinotecan plus nimotuzumab group (HR 0.341; $P = 0.1293$), and the OS was 229.5 days and 358.5 days respectively (HR 0.369; $P = 0.0944$). On the basis of this subgroup analysis in the randomized phase II trial, a phase III trial (NCT01813253) of second-line chemotherapy is currently under way in EGFR 2+/3+ patients with AGC.

Signal transducer and activator of transcription 3 inhibitor

Signal transducer and activator of transcription 3 (STAT3), a transcription factor, is constantly activated in many cancer cells, and the inhibition of STAT3 activation is known to inhibit the growth of cancer cell lines [55, 56]. BBI-608, an orally administered anticancer agent against STAT3 that is designed to inhibit cancer stem cell pathways, is being developed for the treatment of various types of cancer. In a phase I trial of a combination of weekly paclitaxel and BBI-608 in patients with solid cancer, five patients with gastric or EGJ cancer were enrolled. Tumor reduction was observed in three of the five patients (45%, 48%, and 24% respectively), and stable disease was maintained in two patients for 5 months or more [57]. In a phase I trial in six Japanese patients with gastric or EGJ cancer, the response rate was 33.3%, and one of the six patients was reported to maintain the response for 7.5 months or more [58]. A global phase III trial (NCT02178956) is under way in patients with AGC to compare weekly paclitaxel plus BBI-608 with weekly paclitaxel as second-line chemotherapy.

Immune checkpoint inhibitors

The programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway, an immune checkpoint, is involved in the regulation of cellular immune function. In recent years, anti-PD-1 antibodies and anti-PD-L1 antibodies, inhibitors of this pathway, have been actively developed. In particular, anti-PD-1 antibodies demonstrated their high efficacy compared with conventional cytotoxic antitumor agents or ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 antibody approved in the USA in 2011, and are widely used in clinical practice. Currently, pembrolizumab and nivolumab are being developed as anti-PD-1 antibodies for the treatment of AGC (Table 3). As of November 2016, pembrolizumab, a PD-1 antibody, was approved by the FDA for treatment of melanoma, non-small-cell lung cancer and head and neck cancer, and nivolumab was also approved by the FDA for treatment of non-small-cell lung cancer, melanoma, renal cell carcinoma and Hodgkin lymphoma.

Pembrolizumab was evaluated in a phase Ib trial (KEYNOTE-012) for heavily pretreated patients with PD-L1-positive AGC. Of 162 patients screened, 65 patients (40%) were found to be positive for PD-L1. In the trial, 39 of the 65 patients were enrolled and the overall response rate was 22% (8 of the 36 patients achieved response). The median PFS and the median OS were 1.9 months (95% CI 1.8–3.5 months) and 11.4 months (95% CI 5.7 months to not reacted) respectively [59]. A phase III trial (KEYNOTE-061) of second-line chemotherapy for PD-L1-positive patients is being conducted to compare paclitaxel given weekly and pembrolizumab (NCT02370498). If the superiority of pembrolizumab over paclitaxel given weekly is demonstrated in the trial, basic second-line chemotherapy for PD-L1-positive patients with AGC could be replaced by pembrolizumab and standard treatments could undergo a major change. Given that its clinical positioning relative to weekly paclitaxel plus ramucirumab, the current standard chemotherapy, is still unknown, further investigation of pembrolizumab will be needed.

A phase I/II trial (CheckMate-032) evaluated the efficacy and safety of nivolumab as a single agent and in combination with ipilimumab in patients with AGC or advanced EGJ cancer [60]. Fifty-nine patients received treatment with nivolumab, and the overall response rate was 14% (1 complete response, 7 partial responses) and the median OS was 5.0 months (95% CI 3.4–12.4 months).

The trial enrolled patients irrespective of their PD-L1 status. The overall response rate was 27% when the cutoff for PD-L1 positivity was set at 1% or more and 33% when the cutoff was set at 5% or more. Nivolumab is being evaluated in a phase II trial (NCT02746796) as first-line immunotherapy and in a phase III trial (NCT02267343) as third-line immunotherapy. However, no clinical trials of nivolumab as second-line immunotherapy have been conducted.

Avelumab, an anti-PD-L1 antibody, has also been developed for the treatment of patients with AGC. Although the JAVELIN Gastric 100 trial (NCT02625610) of first-line immunotherapy and the JAVLIN Gastric 300 trial (NCT02625623) of third-line immunotherapy are being conducted, no clinical trials of avelumab as second-line immunotherapy have been conducted.

Future perspectives

Second-line chemotherapy should be offered to patients who are maintaining good performance status because its superiority over BSC has been reported on the basis of data from a number of phase III trials [30–32]. Whereas first-line treatment strategies for patients with AGC differ depending on the country, weekly paclitaxel in combination with treatment with ramucirumab, a molecular targeted agent, has been established as standard second-line chemotherapy on the basis of data from past clinical developments. Although the proportion of patients receiving second-line chemotherapy differs depending on the country, clinical developments for second-line and later-line chemotherapy should be continued to achieve further prolongation of survival.

It is also important to develop cytotoxic anticancer agents. Currently, first-line chemotherapy with TAS-118 (SOLAR; NCT02322593), IMAB362 (FAST; NCT01630083), and intraperitoneally administered paclitaxel (Phoenix-GC; UMIN000005930) and third-line chemotherapy with TAS-102 (TAGS; NCT02500043) are being evaluated in clinical trials. They may become promising second-line chemotherapeutic agents depending on the results of the trials. Similarly, immune checkpoint inhibitors are also developed mainly as first-line or third-line therapy. Depending on the results of the KEYNOTE-061 trial, however, standard second-line therapy may undergo a major change, and other immune checkpoint inhibitors may be more actively developed.

Compliance with ethical standards

This article does not contain any studies with human or animal subjects performed by the author. Also, in all studies cited it was declared that informed consent was obtained from all patients for their being included in the studies.

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