ANTICANCER RESEARCH *35*: 4575-4584 (2015)

Review

Second-line Treatment of Advanced Gastric Cancer: Current Options and Future Perspectives

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Abstract. *Due to its high incidence and poor prognosis, gastric cancer is an important health problem worldwide. The only possible curative treatment is to remove the primary tumor at an early stage of the disease. However, at diagnosis, most patients have unresectable or metastatic disease. Relapse in patients after primary surgery is frequent. In these patients, the aim of treatment is to extend the duration of survival and to improve quality of life and this accomplished by systemic therapies. Regimens containing fluoropyrimidine and platinum agents, in combination with trastuzumab in patients with overexpression of human epidermal growth factor receptor 2 (HER2), are recommended as the first-line treatment. Unfortunately, all patients develop progressive disease, but at least half of them are eligible for further treatment. This article presents current possibilities and near-future developments of chemotherapy and molecular targeted-therapy in patients with advanced gastric cancer after failure of prior regimens containing fluoropyrimidine and platinum.*

Gastric cancer is the fifth most common type of cancer and the second leading cause of death from malignant disease worldwide. The highest incidence and mortality rates are reported in Asia, Eastern Europe and South America. It is most frequently diagnosed during the sixth and seventh decade of life and almost two-times more often in men than in women (1). At the time of diagnosis, patients with disease limited to the stomach were found to constitute 26%, patients with involved regional lymph nodes 29% and patients with distant metastases 35% of total number of patients. The 5-year relative survival rates in these groups were 64.1%, 28.8% and 4.2%, respectively (2). Surgical resection of the tumor in the early stage of the disease is the only potentially curative method of treatment. However, due to early oligosymptomatic clinical course, most patients at diagnosis suffer from inoperable or metastatic disease. Moreover, recurrence occurs in half patients who undergo curative gastrectomy (3). In patients with advanced gastric carcinoma (AGC), palliative treatment is used to improve survival and quality of life and is based on chemotherapy and molecular-targeted therapies. Nowadays, regimens containing both fluoropirymidine and platinum, combined with trastuzumab in 10-15% of patients who show overexpression of human epidermal growth factor receptor 2 (HER2), are widely used in the first-line setting (4-7). Unfortunately, all patients develop progressive disease after median of about six months but at least half of them are candidates for receiving second-line treatment (8, 9). Clinical and pathological prognostic factors in patients who may benefit further treatment were described. Eastern Cooperative Oncology Group performance status >1, hemoglobin level <11.5 g/dl, carcinoembryonic antigen level >50 ng/ml, ≥3 metastatic sites and time-to-progression (TTP) of the first-line treatment of less than 6 months were associated with worse prognosis. Patients with one or two such factors had two-fold higher, and patients with three to five such factors had three-fold higher risk of death than patients with none of these factors (10). The development of first-line treatment based on fluoropyrimidine and platinum agents forced the use of second-line regimens containing substances of previously unused groups. We present possibilities for second-line systemic therapy in these patients. Prospective studies that introduced various regimens into today's practice are listed in Table I. Novel agents and regimens that are now being investigated in phase III trials are listed in Table II.

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Key Words: Advanced gastric cancer, second-line, chemotherapy, molecular targeted therapy, review.

Chemotherapy

Irinotecan-containing regimens. Irinotecan is an analog of the natural alkaloid, camptothecin. It inhibits the function of topoisomerase I which is essential in DNA replication. It is used as a single agent or, more frequently, is combined with other

Table I. *Phase II/III trials in the second-line treatment in patients with advanced gastric cancer after failure of therapy based on fluoropyrimidine/platinum.*

Author	No. of pts	Second-line	Third-line (%)	PFS/ TTP (months)	OS (months)	ORR (%)	DCR (%)
Assersohn *et al.* (13)	38	IRI (180 mg/m^2 D1) + LV (125 mg/m^2 D1) + 5-FU (400 mg/m^2 D1 + 1200 mg/m^2 D1,2) *q2w*	NR	3.7	6.4	29	63
Kim *et al.* (14)	57	IRI (150 mg/m^2 D1) + LV (100 mg/m^2 D1) + 5-FU (1000 mg/m^2 D1,2) *q2w*	NR	2.5	7.6	21	46
Giuliani *et al.* (17)	38	IRI (150 mg/m^2 D1,15) + MMC (8 mg/m^2 D1) *q4w*	NR	4.0	8	32	53
Hartmann *et al.* (32)	34	MMC (10 mg/m^2 D1,22) + 5-FU (2600 mg/m^2) + FA (500 mg/m^2) D1,8,15,22,29,36 *q7w*	NR	3.3	7.2	27	56
Kodera *et al.* (26)	45	PXL (80 mg/m^2 D1,8,15) *q4w*	NR	2.6	7.8	16	48
Lee *et al.* (29)	49	DXL (75 mg/m^2) *q3w*	NR	2.5	8.3	16	57
Leary *et al.* (16)	29	IRI (250 mg/m^2 D1) + CP (2x1000 mg/m^2 D1-14) *q3w*	NR	3.1	6.4	17	41
Hamaguchi *et al.* (18)	45	IRI (150 mg/m^2) + MMC (5 mg/m^2) *q2w*	NR	4.1	10.1	29	67
Thuss-Patience *et al.* (12)	21	IRI (250-350 mg/m^2) *q3w*	NR	2.5	4.0*	0	53
	19	BSC	NR	NE	2.4*	NE	NE
Kang *et al.* (31)	66	DXL (60 mg/m^2) *q3w*	40	NE	5.2	11	38
	60	IRI (150 mg/m^2) *q2w*	22	NE	6.5	8	43
	62	BSC	NR	NE	3.8	NE	NE
Fuchs *et al.* (34)	238	RAM (8 mg/kg) *q2w*	32	2.1*	5.2*	3	49*
	117	BSC	39	1.3*	3.8*	3	23*
Sym *et al.* (15)	29	IRI (150 mg/m^2) *q2w*	52	2.2	5.8	17	48
	30	IRI (150 mg/m^2) + LV (20 mg/m^2) + 5-FU (2000 mg/m^2) *q2w*	57	3.0	6.7	20	57
Hironaka *et al.* (27)	108	PXL (80 mg/m^2, D1,8,15) *q4w*	90	3.6	9.5	21	NR
	111	IRI (150 mg/m^2) *q2w*	72	2.3	8.4	14	NR
Ueda *et al.* (19)	22	MMC (5 mg/m^2) + IRI (150 mg/m^2) *q2w*	86	3.9	9.6	19	86
	24	IRI (150 mg/m^2) *q2w*	78	3.7	8.7	10	62
Miranda *et al.* (33)	39	MMC (10 mg/m^2 D1) + CP (2x1000 mg/m^2 D1-14) *q3w*	NR	2.8	5.6	10	44
Ford *et al.* (30)	84	DXL (75 mg/m^2) *q3w*	8	3.0	5.2*	7	53
	84	BSC	19	NE	3.6*	NE	NE
Wilke *et al.* (35)	330	RAM (8 mg/kg D1,15) + PXL (80 mg/m^2 D1,8,15) *q4w*	48	4.4*	9.6*	28*	80*
	335	PXL (80 mg/m^2 D1,8,15) *q4w*	46	2.9*	7.4*	16*	64*
Higuchi *et al.* (20)	64	IRI (60 mg/m^2) + CIS (30 mg/m^2) *q2w*	75	3.8*	10.7	22	75*
	66	IRI (150 mg/m^2) *q2w*	75	2.8*	10.1	16	54*
Satoh *et al.* (36)	132	PXL (80 mg/m^2 D1,8,15) *q4w* + LAP (1500 mg) daily	55	5.5	11.0	27*	NR
	129	PXL (80 mg/m^2 D1,8,15) *q4w*	55	4.4	8.9	9*	NR

PFS: Progression-free survival, OS: overall survival, ORR: objective response rate, DCR: disease control rate, TTP: time to progression, D: day, q: every, w: week, NR: not reported, NE: not evaluated, CIS: cisplatin, IRI: irinotecan, LV: leucovorin, 5-FU: 5-fluorouracil, MMC: mitomycin C, FA: folinic acid, PXL: paclitaxel, DXL: docetaxel, CP: capecitabine, RAM: ramucirumab, LAP: lapatinib, BSC: best supportive care, *statistically significant difference.

cytotoxic drugs. Irinotecan administered weekly at 125 mg/m^2 in patients after failure of previous therapy based on cisplatin and fluoropyrimidine showed decent efficacy [median TTP=2.6 months, median overall survival (OS)=5.2 months and objective response rate (ORR)=20%] with unacceptable hematological toxicity (grade 3-4 neutropenia, anemia and leukopenia were observed in 68%, 57% and 46% of patients, respectively) (11). In the study of Thuss-Patience *et al.*, irinotecan administered three-weekly at 350 mg/m^2 prolonged survival compared to best supportive care [4.0 *vs.* 2.4 months, hazard ratio (HR)=0.48, p=0.012] in patients with gastric (57%) or gastroesophageal junction (GEJ) cancer (43%) who developed progression during cisplatin-based therapy. Computed tomographic scans were performed only in the irinotecan-treated group, therefore progression-free survival (PFS) was not reported in the control arm. Adverse events of grade 3 or 4 were less frequent than in patients treated with a weekly schedule (diarrhea: 26%, leucopenia: 21%). Improvement in tumor-related symptoms was observed in 50% cases in the treatment arm and 7% in the control arm, however, no validated tool was used to assess it. Concomitantly, it was the first prospective trial that compared anti-neoplastic regimen with best supportive care only and showed that second-line chemotherapy is an effective strategy for AGC (12).

Table II. *Ongoing phase III trials in the second-line treatment of advanced gastric cancer after failure of therapy based on fluoropyrimidine and platinum.*

ClinicalTrials.gov identifier	Investigational arm	Control arm
NCT01641939 (47)	T-DM1	Taxane
NCT01813253 (50)	Nimotuzumab + irinotecan	Irinotecan
NCT01924533 (53)	Olaparib + paclitaxel	Placebo + paclitaxel
NCT02178956 (55)	BBI608 + paclitaxel	Placebo + paclitaxel
NCT01839773 (57)	DHP107	Paclitaxel
NCT01573468 (59)	Tesetaxel + capecitabine	Placebo + capecitabine
NCT01248403 (60)	Everolimus + paclitaxel	Placebo + paclitaxel

T-DM1: Trastuzumab emtansine, BBI608: cancer stem cell inhibitor, DHP107: oral paclitaxel.

In the study of Assersohn *et al*., a bi-weekly combination of irinotecan and leucovorin plus bolus of 5-fluorouracil (5-FU) followed by continuous intravenous infusion of 5-FU was applied to patients with unresectable esophageal (39%), GEJ (24%) or gastric cancer (37%) who failed prior therapy based on platinum. Fairly high activity (29% objective responses, median PFS reaching 3.7 months) was associated with neutropenia (26%), infections and lethargy (16% each) as most frequent grade 3 or 4 toxicities. Febrile neutropenia occurred in 5% of cases. The authors also showed that the treatment was associated with improvement in tumor-related symptoms (13). A similar regimen with lower doses of agents was tested by Kim *et al*. in patients with metastatic adenocarcinoma of the stomach who were previously treated with cisplatin and taxane. Among assessable patients, objective responses and stable disease were observed less frequently than in the study of Assersohn *et al*. but grade 3 and 4 toxicity was also lower (neutropenia: 11%, thrombocytopenia: 8%, febrile neutropenia: 3%) (14).

Sym *et al*. showed in a randomized phase II trial that addition of 5-FU and leucovorin to irinotecan in a bi-weekly schedule did not improve efficacy in terms of median PFS (2.2 months in monotherapy *vs*. 3.0 months in combined therapy, HR=1.20, p=0.481), median OS (5.8 *vs*. 6.7 months, HR=1.21, p=0.514) and ORR (17% *vs*. 20%, p=0.525). No significant difference was observed in grade 3-4 adverse events (21 *vs*. 28 cases, p=0,067). However, only 59 patients with metastatic GEJ or gastric adenocarcinoma participated in the study in both arms, hence any possible superiority of combined treatment over monotherapy could not be detected (15).

Irinotecan was also tested in combination with capecitabine, an oral prodrug of 5-FU, in patients with unresectable squamous cell carcinoma or adenocarcinoma of the esophagus (45%), GEJ (38%), or stomach (17%) who failed prior platinum-based chemotherapy. Efficacy of this therapy was similar to that of irinotecan plus 5-FU regimens. Improvement in disease-related symptoms was observed as was an increase in global and functional quality-of-life scores. Most common grade 3 or 4 toxicities were neutropenia and lethargy (31% each) (16).

Regimens containing irinotecan and mitomycin C were assessed in few phase II trials in patients with AGC. In the study of Giuliani *et al*., after failure of previous therapies including cisplatin and fluoropirimidine, patients received biweekly irinotecan plus mitomycin C at a dose of 8 mg/m^2 every 4 weeks (17). Hamaguchi *et al*. used similar regimen but with mitomycin C at a dose of 5 mg/m^2 administered biweekly in patients with fluoropyrimidine-resistant disease (18). Median TTP/PFS reached 4 months and ORR was about 30% in both studies. Toxicity included mainly hematological disturbances, which happened more often in Hamaguchi *et al*.'s study. In a non-randomized trial, there was no significant increase in efficacy of biweekly regimen containing irinotecan plus mitomycin C than irinotecan alone, however, significant differences might not have been found due to a small number of patients who participated in the study. Grade 3 or 4 neutropenia (45% *vs*. 25%), anemia (36% *vs*. 4%), febrile neutropenia (14% *vs*. 8%), anorexia (14% *vs*. 8%) tended to be higher in patients receiving combined treatment (19).

Higuchi *et al*. conducted a randomized phase III study of biweekly irinotecan plus cisplatin *versus* irinotecan alone in patients with metastatic or recurrent gastric cancer refractory to S-1-based first-line chemotherapy, mainly combined with platinum. The median PFS was significantly higher for patients receiving combined therapy than those receiving irinotecan alone (3.8 *vs*. 2.8 months, HR=0.68, p=0.0398). However, there was no significant difference in median OS (10.7 *vs*. 10.1 months, HR=1.00, p=0.9823) or ORR (22% *vs*. 16%, p=0.4975). The incidences of grade 3 and 4 adverse events did not differ between the two groups. A total of 75% of patients in each group received third line-chemotherapy (20).

Taxane-containing regimens. Taxanes, paclitaxel and docetaxel bind microtubules of the mitotic spindle. This leads to inhibition of mitosis and directs the cell to apoptosis. Paclitaxel was used in monotherapy of AGC in a three-

weekly schedule at doses ranging from 200 to 225 mg/m^2 (21-23). However, pharmacokinetic studies and clinical reports for other types of neoplasms showed less toxicity and greater effectiveness of weekly administration of paclitaxel at lower doses (24, 25). Kodera *et al*. tested weekly paclitaxel at 80 mg/m^2 in patients whose disease was refractory to fluoropyrimidine and the reported median PFS was 2.6 months, while partial responses were observed in 16% of cases. The most frequent grade 3 or 4 toxicities were leukopenia and neutropenia, occurring in 18% and 16% of patients, respectively (26). Hironaka *et al*. performed a phase III study to compare weekly paclitaxel with bi-weekly irinotecan in patients with disease resistant to previous therapy containing fluoropyrimidine plus platinum. A total of 219 patients who were eligible for analysis underwent randomization in a 1:1 ratio. No statistically significant difference was found between paclitaxel- and irinotecan-treated groups for median PFS (3.6 *vs*. 2.3 months, HR=1.14, p=0.33), median OS (9.5 *vs*. 8.4 months, HR=1.13, p=0.38), and ORR (21% *vs*. 14%, p=0.24, respectively). Most common grade 3 or 4 adverse events were neutropenia (29% with paclitaxel *vs*. 39% with irinotecan) and anemia (21% *vs*. 30%, respectively). Patients in the irinotecan-treated group developed febrile neutropenia three times more often than patients in the paclitaxel-treated group (9% *vs*. 3%). It should be noted that patients recruited in the study were in good condition and had no severe peritoneal metastases, thus, most of them received third-line chemotherapy (27).

On the other hand, weekly docetaxel disappointed as second-line chemotherapy in AGC, according to the study of Graziano *et al*., where patients treated with docetaxel administered at 36 mg/m^2 achieved a median OS of 3.6 months, with only one partial response (28). Meanwhile, Lee *et al*. justified the use of three-weekly docetaxel at 75 mg/m^2 in patients after failure of fluoropyrimidine plus platinum chemotherapy, but also reported a high frequency of febrile neutropenia (19%) related to this treatment (29). The same regimen was repeated in a randomized phase III study by Ford *et al*., where patients in docetaxel arm achieved statistically significant improvement in median OS than patients in the active symptom control arm (5.2 *vs*. 3.6 months, HR=0.67, p=0.01). Moreover, patients treated with docetaxel reported less pain (p=0.0008), less nausea and vomiting (p=0.02) and less constipation (p=0.02). Incidence of grade 3 or 4 adverse events was higher in the treatment arm than in the control arm (neutropenia: 15% of patients *vs*. no patients, infection: 19% *vs*. 3%, febrile neutropenia: 7% *vs*. no patients, respectively) (30).

Kang *et al*. compared three-weekly docetaxel at 60 mg/m^2 *versus* biweekly irinotecan at 150 mg/m^2 *versus* best supportive care only in 188 patients with AGC with one or two prior chemotherapy regimens involving both fluoropyrimidine and platinum. The median OS was 5.3 months among the 133 patients in both treatment arms and 3.8 months among 69 patients in the observational arm (HR=0.657; p=0.007). However, no statistically significant difference in survival was found between the docetaxel-treated and irinotecan-treated groups (5.2 *vs*. 6.5 months, respectively; p=0.116) (31).

Mitomycin C-containing regimens. Mitomycin C, a natural antibiotic, is also a multifunctional alkylating agent. The drug inhibits DNA synthesis and cross-links DNA. Attempts to repair DNA lead to strand breaks. In addition to the previously mentioned combination with irinotecan, mitomycin C may be used with fluoropyrimidines for AGC. Hartmann *et al*. showed high activity but with average median TTP and OS of a regimen containing mitomycin C plus folinic acid and 5-FU in patients after one or two prior chemotherapies. Most common grade 3 or 4 adverse events were thrombocytopenia (16%), mucositis and diarrhea (9% each) (32). In the study by Miranda *et al*., 5-FU was replaced by capecitabine. Efficacy was slightly lower than in the study of Hartmann *et al*. but the profile and frequency of grade 3 and 4 toxicities were similar (33). In these studies, the total dose of mitomycin C was limited to 50 mg/m^2 due to the risk of pulmonary fibrosis and hemolytic-uremic syndrome.

Molecular Targeted Therapy

Disturbances in genes and cellular signaling pathways observed in many types of malignancies are widely studied as therapeutic targets. Currently, ramucirumab, a fully human monoclonal antibody (IgG1) directed against vascular endothelial growth factor receptor 2 (VEGFR2) is the only molecular-targeted drug approved in the second-line therapy of gastric cancer. It was tested in two large, double-blinded phase III trials. In the REGARD study 355 patients with advanced gastric (75%) or GEJ carcinoma (25%) and disease progression after first-line platinum- or fluoropyrimidine-containing chemotherapy were randomly assigned in a 2:1 ratio to receive best supportive care plus either ramucirumab or placebo. Patients in the ramucirumab arm achieved significantly longer median PFS (2.1 *vs*. 1.3 months, HR=0.46, p<0.001) and median OS (5.2 *vs*. 3.8 months, HR=0.78, p=0.047) than patients in the placebo arm. Objective responses were low in both groups. Rates of adverse events were mostly similar for the two groups, except hypertension, which occurred more frequently in the ramucirumab arm than in the placebo arm (16% *vs*. 8%). After six weeks from treatment initiation, a larger proportion of patients in the ramucirumab group reported stable or improved global quality of life than those in the placebo group; however, this difference was not statistically significant (34). In the RAINBOW trial, 665 patients with advanced gastric (80%) or GEJ adenocarcinoma (20%) and disease progression on or

within 4 months after first-line chemotherapy (platinum plus fluoropyrimidine with or without an anthracycline) were randomized in a 1:1 ratio to receive paclitaxel plus either ramucirumab or placebo. The median OS was higher in the investigational arm than in the control arm (9.6 *vs*. 7.4 months, HR=0.81, p=0.017) as was the median PFS (4.4 *vs*. 2.9 months, HR=0.635, p<0.001). Moreover, ramucirumab plus paclitaxel was more active than placebo plus paclitaxel. Grade 3 and 4 adverse events were more common in the ramucirumab group than in the placebo group (neutropenia: 41% *vs*. 19%; hypertension: 14% *vs*. 2%; fatigue: 12% *vs*. 5%, respectively). Baseline and end-of-treatment results for global quality of life were similar in the treatment groups. Almost half of the patients in both arms received third-line treatment. However, this percentage was higher in the Asian population (nearly 70%) than in other populations (European, North and South American, almost 40%), thus, it could lead to longer survival of Asian patients than those in other regions (35).

Lapatinib, a dual-tyrosine kinase inhibitor which interrupts the epidermal growth factor receptor (EGFR) and HER2, was tested in Asian patients who were HER2 positive by fluorescence *in situ* hybridization after failure of first-line chemotherapy. A total of 261 patients randomized in a 1:1 ratio received lapatinib-plus-paclitaxel or paclitaxel-alone. No significant difference was found in median PFS and OS. However, in the subgroup analysis, better efficacy with lapatinib plus paclitaxel was demonstrated in patients with an immunohistochemistry (IHC) score 3+ compared with those with IHC score 0/1+ or 2+. It should be also noted that about 95% of patients in both arms did not receive trastuzumab in the first-line therapy (36).

Everolimus, an oral inhibitor of mammalian target of rapamycin was tested at 10 mg a day in a randomized phase III GRANITE-1 study. Compared with best supportive care, it did not improve outcomes for patients whose disease progressed after one or two lines of previous systemic chemotherapy (37).

Sunitinib, an oral multi-targeted receptor tyrosine kinase inhibitor administered by standard schedule (50 mg a day for 4 consecutive weeks, then 2 weeks without drug) showed poor efficacy in two phase II trials (38, 39). In a randomized phase II study, sunitinib used at 37.5 mg daily with three-weekly docetaxel was not superior to docetaxel alone in terms of median TTP and OS (40).

Sorafenib, another oral multi-targeted receptor tyrosine kinase inhibitor, was rejected due to low response rates and no evidence of improvement in median PFS or OS, both as a single agent and in combination with oxaliplatin, according to phase II studies (41, 42).

Other molecular-targeted drugs, bevacizumab, cetuximab and panitumumab, also did not improve outcomes in the first-line therapy of AGC (43-45) and have not been widely studied in the second-line setting.

Novel Agents and Regimens

With median PFS ranging from 3 to 4 months and ORR not exceeding one-third of patients, current options for the second-line treatment of AGC remain insufficient. Thus, new agents and drug combinations with promising results in preclinical and phase I studies are being investigated in phase III trials.

Trastuzumab emtansine (T-DM1), an antibody–drug conjugate consisting of trastuzumab and cytotoxic agent DM1 is approved for advanced HER2-positive breast cancer in women whose disease is already resistant to trastuzumab (46). Now it is being evaluated in patients with HER2-positive gastric or GEJ adenocarcinoma who experience disease progression during or after fluoropyrimidine- and platinum- based first-line therapy. Prior therapy does not need to have included HER2-directed therapy. Patients are randomized to one of three arms: T-DM1 at 3.6 mg/kg every 3 weeks, T-DM1 at 2.4 mg/kg every week, or physicians choice of paclitaxel or docetaxel (47).

Nimotuzumab, a monoclonal antibody against EGFR, was found to be effective against squamous cell carcinoma of the head and neck (48). In a phase II study, nimotuzumab at 400 mg weekly plus biweekly irinotecan showed no superiority over irinotecan monotherapy in patients with AGC, however, an improvement in PFS, OS, and ORR was seen in subgroup of patients with EGFR overexpression (IHC score 2+ or 3+) (49). Based on these results, a phase III trial is being conducted in patients with EGFR-overexpressing advanced gastric or GEJ cancer who failed on first-line therapy consisting of 5-FU and platinum (50).

Olaparib, an inhibitor of poly ADP ribose polymerase (PARP), an enzyme involved in DNA repair, is approved for women with platinum-sensitive, recurrent, high-grade serous ovarian cancer and mutation of breast cancer gene (BRCA) (51). In a phase II study, patients with recurrent or metastatic gastric cancer who received second-line therapy consisting of olaparib and paclitaxel achieved increased survival when compared to patients receiving paclitaxel alone (13.1 *vs*. 8.3 months, HR=0.56; p=0.010), without a difference in median PFS (52). This led investigators to continue research in a placebo-controlled phase III trial in an Asian population (53).

BBI608 is an oral first-in-class cancer stem cell inhibitor which inhibits signal transducer and activator of transcription 3, β-catenin and Nanog transcription factor pathways. Encouraging antitumor activity of BBI608 plus paclitaxel was observed across several tumor types, particularly in patients with gastric and GEJ adenocarcinoma (54). A study to determine if weekly paclitaxel given together with twice daily BBI608 at 480 mg as second-line therapy will prolong survival compared to paclitaxel alone is currently recruiting (55).

In a phase II trial, DHP107, an oral paclitaxel, administered twice daily at 200 mg/m^2 was generally well tolerated and showed antitumor activity comparable to intravenous

paclitaxel as a second-line chemotherapy in AGC (56). Based on these results, a phase III study is ongoing (57).

Tesetaxel is a new oral taxane that is not a substrate for P-glycoprotein, a major cause of taxane resistance in tumor models. As a single agent, it is not associated with hypersensitivity and causes less neuropathy compared to standard taxanes without a decrease in antitumor activity (58). Combination of capecitabine at 1750 mg/m^2/day on days 1-14 plus tesetaxel at 27 mg/m^2 once on day 1 or placebo in a 21-day cycle is now being investigated (59).

Conclusion

Recent years have greatly expanded our understanding over the palliative treatment of AGC after failure of first-line therapy based on fluoropyrimidine and platinum agents. Primarily, it was demonstrated that the continuation of systemic treatment in eligible patients prolongs survival and may improve quality of life when compared to best supportive care only. Sufficient antitumor activity and acceptable toxicity is observed in monotherapies with irinotecan, paclitaxel, docetaxel and ramucirumab and combination regimens containing irinotecan plus fluoropyrimidine, irinotecan plus mitomycin C, mitomycin C plus fluoropyrimidine, and ramucirumab plus paclitaxel. Significant increase in efficacy was shown only for ramucirumab plus paclitaxel compared with paclitaxel alone. Moreover, second-line treatment may improve a patient's quality of life and relieve disease-related symptoms. However, the efficacy of currently used therapies is still highly unsatisfactory. Ongoing phase III trials that focus on anti-HER2 and anti-EGFR therapies, PARP and cancer stem cell inhibitors, and oral taxanes may bring more efficient options in the near future.

Conflicts of Interest

None declared.

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Received May 12, 2015
Revised June 14, 2015
Accepted June 16, 2015