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Current status of doublet combinations of platinum and fluoropyrimidines using oxaliplatin for advanced gastric cancer

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Abstract: The most common treatment for advanced gastric cancer (AGC) is systemic chemotherapy. The standard treatment for advanced gastric cancer differs worldwide. In Japan, two phase III clinical trials demonstrated the non-inferiority of S-1 compared with 5-fluorouracil (5-FU) and superiority of cisplatin plus S-1 (CS), compared with S-1, with respect to overall survival (SPIRITS trial). Oxaliplatin (L-OHP) has a favorable toxicity profile compared with cisplatin; hence, a phase III clinical trial (G-SOX trial) demonstrated the progression-free survival (PFS) and overall survival in CS was 5.4 and 13.1 months and those in SOX was 5.5 and 14.1 months, respectively. Serious adverse events were more frequently seen in CS than in SOX. So, SOX is as effective as CS for advanced gastric cancer with favorable safety profile. After the publication of this G-SOX trial, the combination of oral or intravenous 5-FU and various doses of L-OHP have been reported. And FOLFOX6 regimen (FOLFOX: a combination of l-LV and FU with L-OHP) was approved for the treatment of AGC in Japan in 2017. FOLFOX was promising for patients with severe peritoneal metastasis from AGC, because the FOLFOX regimen does not require hydration and does not include oral agents. This review summarizes the efficacy and safety of doublet combinations of platinum and fluoropyrimidines using L-OHP for advanced gastric cancer.

Keywords: advanced gastric cancer, oxaliplatin, S-1, FOLFOX

Introduction

Gastric cancer is the fifth most common type of malignancy in the world and the third common cause of cancer mortality worldwide (*1*). The prevalence of gastric cancer is highest in East Asia. The treatment options for gastric cancer, such as surgery, chemotherapy, and radiotherapy, dependently vary on the tumor status. The mainstay of the treatment for advanced gastric cancer (AGC) is systemic chemotherapy. In the 1990s, prospective clinical trials and meta-analyses were conducted, which indicated the better prognosis of systemic chemotherapy, compared with the best supportive care (*2-5*).

S-1 is an oral anti-cancer preparation that combines tegafur, a pro-drug of 5-fluorouracil (5-FU), with two modulators, namely, gimeracil and oteracil (*6*). In Japan, two phase III clinical trials conducted by the Japan Clinical Oncology Group (JCOG) demonstrated the non-inferiority of S-1 compared with 5-FU and the superiority of cisplatin plus S-1 (CS) compared with S-1, with respect to overall survival (OS) (SPIRITS trial) (*7,8*). After these trials, CS was regarded as the standard first-line AGC treatment in Japan (*9*).

Oxaliplatin (L-OHP) is a third-generation platinum-based compound that has tolerability and ease of administration, compared with cisplatin. Several phase II studies have addressed the usefulness of the S-1 plus L-OHP (SOX) regimen as a first-line therapy at various doses and schedules (*10-14*). A phase III clinical trial (G-SOX trial) conducted by the JCOG demonstrated the efficacy and safety of SOX as a CS alternative in first-line chemotherapy for AGC (*15*). L-OHP was approved for AGC on the basis of the G-SOX trial in 2014 (*9*). SOX has several advantages in terms of toxicity and administration, compared with CS; hence, SOX has been widely used in clinical practice. This review summarizes the efficacy and safety of doublet combinations of platinum and fluoropyrimidines using L-OHP for AGC treatment.

Dose of L-OHP and efficacy

In a REAL-2 study, a randomized two-by-two phase III study of triplet therapy consisting of epirubicin, 5-FU or capecitabine, and cisplatin or L-OHP showed the non-inferiority of L-OHP (130 mg/m^2 every 3 weeks) to cisplatin (60 mg/m^2 every 3 weeks), with respect to

survival (*16*). In Japan, L-OHP (130 mg/m^2 every 3 weeks) was approved for AGC in 2014, on the basis of the results of the REAL-2 study. However, a phase II trial to evaluate the safety of SOX and a G-SOX trial were conducted using S-1 plus L-OHP (100 mg/m^2) (SOX_{100}). Table 1 shows major clinical trials of first-line chemotherapy, including L-OHP, for AGC. The progression-free survival (PFS) in these two trials using SOX_{100} was 6.5 and 5.5 months, and OS was 16.5 and 14.1 months, respectively (*13,15*). The PFS and OS of CS in a SPIRITS trial were 6.0 and 13.0 months, respectively (*8*). Although the G-SOX trial statistically failed to show the non-inferiority of SOX compared with CS, it was thought that the OS was comparable between the two regimens. A phase II trial to evaluate the feasibility of S-1 plus L-OHP (130 mg/m^2) (SOX_{130}) was conducted because of the lack of data on SOX_{130} for AGC in Japan (*17*). In the trial, the PFS and OS were 5.7 and 13.1 months, respectively. In an SOPP study, a phase III clinical trial to assess the non-inferiority/superiority of SOX_{130} compared with CS in terms of PFS in Korean AGC patients showed that the PFS and CS in SOX_{130} were 5.6 and 5.7 months, and the OS and CS in SOX_{130} were 12.9 and 11.4 months, respectively (*18*). The SOPP study concluded that SOX_{130} was non-inferior to CS, but not superior to CS. Considering the SOPP and the G-SOX trials, the SOX regimen can be one of the standard options for first-line AGC treatment in East Asian countries.

Feasibility and safety of SOX

In the G-SOX trial, L-OHP (100 mg/m^2) was used because of possible bleeding from the primary lesion site and to maintain the S-1 dose intensity. Table 2 summarizes adverse events (AEs) in major clinical trials of first-line chemotherapy, including SOX for AGC. The most common ≥ grade 3 AEs over 10% were neutropenia (19.5%), anorexia (15.4%), anemia (15.1%), and thrombocytopenia (10.1%) (*15*). Among hematologic AEs, leukopenia, neutropenia, and anemia were less observed in SOX_{100} than in CS (4.1% versus 19.4%, 19.5% versus 41.8%, and 15.1% versus 32.5%). The rate of ≥ grade 3 febrile neutropenia was significantly lower in SOX_{100} than in CS (0.9% versus 6.9%). Among the non-hematologic AEs, hyponatremia was seen less in SOX_{100} than in CS (4.4% versus 13.4%). Grade 3 or worse sensory neuropathy was more frequently observed in SOX_{100} than in CS (4.7% versus 0.0%). The difference in AE profiles between SOX_{130} and CS in the SOPP trial was similar to that in the G-SOX trial (*18*). However, there were several differences in AEs between SOX_{100} and SOX_{130}. In the SOPP trial, thrombocytopenia of all grades, and nausea and vomiting of all grades were more common with SOX_{130} than with CS (70.5% versus 57.9%, 56.6% versus 43.3%, and 32.4% versus 20.1%). In the G-SOX trial, nausea of all grades was more frequent with CS than with SOX_{100} (69.0% versus 61.5%). The phase II trials using SOX_{130} for Japanese AGC patients showed that the frequency of ≥ grade 3 thrombocytopenia and nausea of all grades was similar to that of the G-SOX trial (16.0% versus 10.1% and 56.0% versus 61.5%) (*17*). In the HIGHSOX trial, which was a multicenter phase II trial to investigate the efficacy and safety of the combination chemotherapy of trastuzumab plus SOX_{130} for patients with Japanese HER2-positive AGC, the lower rate of ≥ grade 3 thrombocytopenia (all grades, 78.7%; ≥ grade 3, 1.3%) and higher rate of nausea (all grades, 65.3%; ≥ grade 3, 4.0%) were seen, relative to those in G-SOX (*19*). These results indicated that SOX_{130} has a higher frequency of gastrointestinal toxicities, compared with SOX_{100}. In the aforementioned two phase II trials to evaluate the feasibility of SOX_{130}, the dose of L-OHP was reduced if the platelet count was

Table 1. Clinical trials of first-line chemotherapy, including oxaliplatin, for advanced gastric cancer: a summary of major trials

Trial/authors	Phase	Regimens	No. of patients	OS (months)	HR (95% CI)	PFS (months)	HR (95% CI)
REAL-II (*16*)	III	Epirubicin (50 mg/m^2) + cisplatin (60 mg/m^2) + fluorouracil (200 mg/m^2/day)	249	9.9	1 (Reference)	6.2	1 (Reference)
		Epirubicin (50 mg/m^2) + cisplatin (60 mg/m^2) + capecitabine (2,000 mg/m^2/day)	241	9.9	0.92 (0.76-1.11)	6.7	0.98 (0.82-1.17)
		Epirubicin (50 mg/m^2) + oxaliplatin (130 mg/m^2) + fluorouracil (200 mg/m^2/day)	235	9.3	0.96 (0.79-1.15)	6.5	0.97 (0.81-1.17)
		Epirubicin (50 mg/m^2) + oxaliplatin (130 mg/m^2) + capecitabine (2,000 mg/m^2/day)	239	11.2	0.80 (0.66-0.97)	7.0	0.85 (0.70-1.02)
G-SOX (*15*)	III	Cisplatin (60 mg/m^2) + S-1 (80-120 mg/day)	324	13.1	0.958 (0.803-1.142)	5.4	1.004 (0.840-1.199)
		Oxaliplatin (100 mg/m^2) + S-1 (80-120 mg/day)	318	14.1		5.5	
SOPP (*18*)	III	Cisplatin (60 mg/m^2) + S-1 (80-120 mg/day)	164	11.4	0.86 (0.66-1.11)	5.7	0.85 (0.67-1.07)
		Oxaliplatin (130 mg/m^2) + S-1 (80-120 mg/day)	173	12.9		5.6	
Kito *et al.* (*17*)	II	Oxaliplatin (130 mg/m^2) + S-1 (80-120 mg/day)	25	13.1	-	5.7	-

HR, hazard ratio; OS, overall survival; PFS, progression-free survival; 95% CI, 95% confidence interval.

Table 2. Adverse events in major clinical trials of first-line chemotherapy, including SOX, for advanced gastric cancer

Variables	G-SOX (*15*)		SOPP (*18*)		Kito *et al.* (*17*)	HIGHSOX (*19*)
	SOX_{100} (*n* = 338)	CS (*n* = 335)	SOX_{130} (*n* = 173)	CS (*n* = 164)	SOX_{130} (*n* = 25)	SOX_{130} + T-mab (*n* = 75)
Neutropenia						
Any (%)	68.9	79.4	57.2	71.3	68.0	78.7
≥ Grade 3 (%)	19.5	41.8	16.2	39.6	12.0	10.7
Anemia						
Any (%)	55.3	73.7	22.0	29.9	96.0	96.0
≥ Grade 3 (%)	15.1	32.5	5.2	11.0	20.0	6.7
Thrombocytopenia						
Any (%)	78.4	69.3	70.5	57.9	92.0	78.7
≥ Grade 3 (%)	10.1	10.4	7.5	4.9	16.0	1.3
Febrile neutropenia						
Any (%)	0.9	6.9	0.6	4.9	0.0	0.0
≥ Grade 3 (%)	0.9	6.9	0.6	4.9	0.0	0.0
Nausea						
Any (%)	61.5	69.0	56.6	43.3	56.0	65.3
≥ Grade 3 (%)	3.8	3.9	3.5	2.4	4.0	4.0
Vomiting						
Any (%)	34.9	35.5	32.4	20.1	24.0	20.0
≥ Grade 3 (%)	0.6	1.5	1.2	1.8	0.0	4.0
Diarrhea						
Any (%)	48.2	58.5	28.9	22.0	24.0	52.0
≥ Grade 3 (%)	5.6	7.5	4.0	3.7	0.0	6.7
Anorexia						
Any (%)	74.6	80.9	50.9	56.1	92.0	77.3
≥ Grade 3 (%)	15.4	18.5	8.7	6.7	24.0	5.3
Peripheral sensory neuropathy						
Any (%)	85.5	23.6	59.0	34.8	76.0	84.0
≥ Grade 3 (%)	4.7	0.0	8.7	3.7	0.0	16.0

CS, a combination of S-1 and cisplatin; SOX, a combination of S-1 and oxaliplatin; T-mab, trastuzumab.

75,000-100,000/μL on the day of its administration, in accordance with the SOFT trial criteria, which evaluated the non-inferiority between SOX_{130} plus bevacizumab and modified FOLFOX6 plus bevacizumab in terms of the PFS of Japanese patients with advanced colorectal cancer (*20*). These results suggested that the L-OHP dose reduction protocol recommended by the SOFT trial may have contributed to the safer profile, especially thrombocytopenia, compared with that by the G-SOX trial. The safety profile of SOX_{130} was considerably acceptable, although several different patterns of AEs were seen between SOX_{100} and SOX_{130}.

Peripheral sensory neuropathy (PSN) is a common dose-limiting toxicity observed with L-OHP (*21,22*). It is crucial to discontinue L-OHP before developing severe PSN, because there is no effective method for PSN prevention. A retrospective observational study using data from the AGAMENON registry, wherein 31 Spanish centers and 1 Chilean center participated, reported that platinum discontinuation, followed by fluoropyrimidine maintenance, was an effective strategy for first-line chemotherapy for AGC to maintain treatment efficacy, with a low rate of serious AEs (*23*). The "stop-and-go" strategy was also reported as an appropriate approach to reduce the incidence of severe neurotoxicity while maintaining treatment efficacy (*24*). These results suggested that the maintenance strategy, such as discontinuation of L-OHP, followed by fluoropyrimidine maintenance until progression or chemotherapy-free interval, followed by doublet combinations of L-OHP and fluoropyrimidine re-introduction at the progression stage, was a valuable method to reduce AEs while maintaining therapeutic efficacy.

Application of L-OHP for AGC with ascites or inadequate oral intake

Peritoneal metastasis is the most common recurrent or metastatic site for AGC (*25-28*). Peritoneal metastasis from AGC frequently causes complicated ascites, intestinal stenosis/obstruction, paralytic ileus, and ureteral obstruction (hydronephrosis); hence, patients with peritoneal metastasis have poor prognosis, because it is difficult to give the standard treatment for these patients (*29,30*). S-1 or capecitabine, in combination with cisplatin or L-OHP, is the first-line standard treatment regimen for AGC in Japan (*9*). However, oral fluoropyrimidine plus cisplatin cannot be administered to these patients because of inadequate oral intake or renal dysfunction. JCOG0106 demonstrated that methotrexate and 5-FU therapy was not superior to

continuous infusion of 5-FU (OS: 10.6 months versus 9.4 months; hazard ratio: 0.94; 95% confidence interval, 0.72-1.22; one-sided $p = 0.31$) (*31*). On the basis of JCOG0106, 5-FU/l-leucovorin (l-LV) is the drug that is most often administered to this population. However, the efficacy of 5-FU/l-LV is not sufficient, compared with combination chemotherapy of fluoropyrimidine and platinum. After 5-FU/l-LV/L-OHP (FOLFOX) had been approved for AGC in Japan, FOLFOX was promising for patients with severe peritoneal metastasis, because the FOLFOX regimen does not require hydration and does not include oral agents. Table 3 shows prospective or retrospective studies about the safety and efficacy of chemotherapy for AGC with ascites or inadequate oral intake. In JCOG0106, the median OS in the 5-FU group was 9.4 months, and the rate of grade ≥ 3 neutropenia, grade ≥ 3 anorexia, and treatment-related mortality in the 5-FU group were 0.9%, 27.4%, and 1.7%, respectively. An improved oral intake was observed in 41.2% of patients in the 5-FU group. Osumi *et al.* and Masuishi *et al.* conducted retrospective studies to evaluate the modified FOLFOX6 (mFOLFOX6) regimen in patients with AGC with severe peritoneal metastasis, massive ascites, or inadequate oral intake (*32,33*). In those studies, the median PFS and OS were 4.2 and 7.5 months and 8.8 and 13.2 months, respectively. Interestingly, the proportion of patients exhibiting improvement in oral intake were 83.0% and 57.0%, respectively, which were higher than other treatment regimens for the same previously reported population. These findings suggest that mFOLFOX6 is a favorable regimen for patients with AGC with severe peritoneal metastasis, massive ascites, or inadequate oral intake. Neutropenia was the most common AE, and dose modification was required in about half of the patients because of the AEs in each study, because most patients have poor performance status. Furthermore, 5-FU/l-LV plus paclitaxel (FLTAX) is another promising regimen for AGC with severe peritoneal metastasis. However, a randomized phase II/III trial conducted by the JCOG and West Japan Oncology Group showed that FLTAX was not significantly superior to 5-FU/l-LV in terms of OS (*34*). Recently, a multicenter phase II trial evaluating the feasibility and efficacy of mFOLFOX6 for the same population (WJOG10517G: jRCTs041180007) is ongoing in Japan (*35*).

Table 3. Safety and efficacy of chemotherapy for AGC with massive ascites or inadequate oral intake

	JCOG0106 (*31*)	Oh *et al.* (*36*)	Masuishi *et al.* (*33*)	Osumi *et al.* (*32*)	JCOG1108/WJOG7312G (*34*)
Variables	Total ($n = 119$) Number of patients (%)	Total ($n = 48$) Number of patients (%)	Total ($n = 10$) Number of patients (%)	Total ($n = 17$) Number of patients (%)	Total ($n = 50$) Number of patients (%)
Regimen	5-FU	mFOLFOX4	mFOLFOX6	mFOLFOX6	FLTAX
Age (year)					
Median	61	60	64.5	67	65
Range	(31-75)	(60-70)	(40-94)	(29-74)	(29-75)
Sex					
Male	66 (55.5)	32 (66.7)	2 (20.0)	6 (35.3)	30 (60.0)
ECOG PS					
≥ 2	4 (3.4)	22 (45.8)	5 (50.0)	4 (23.5)	14 (28.0)
No. of metastatic sites					
≥ 2	40 (33.6)	18 (37.5)	5 (50.0)	12 (70.6)	NE
Prior chemotherapy					
≥ 1	0 (0.0)	27 (56.2)	0 (0.0)	0 (0.0)	0 (0.0)
Measurable lesion					
Yes	NE	30 (62.5)	3 (30.0)	10 (58.8)	NE
Ascites					
Yes	84 (70.6)	48 (100.0)	9 (90.0)	12 (70.6)	32 (64.0)
Inadequate oral intake					
Yes	17 (14.3)	NE	7 (70.0)	13 (76.4)	27 (54.0)
Improvement in oral intake					
Yes	7 (41.2)	NE	4 (57.0)	11 (83.0)	10 (37.0)
Relative dose intensity (%)					
L-OHP or paclitaxel	NE	95.5	64	90	82.5
5-FU		97.7 (total)	62 (bolus) 77 (ci)	63.4 (bolus) 99.7 (ci)	83 (total)
Response					
RR	NE	12 (33.3)	3 (100.0)	5 (50.0)	NE
DCR		25 (69.4)	3 (100.0)	6 (60.0)	
PFS (months)	NE	3.5	7.5	4.2	5.4
OS (months)	9.4	8.4	13.2	8.8	7.3

DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FLTAX, a combination of l-leucovorin and fluorouracil with paclitaxel; FOLFOX, a combination of l-leucovorin and fluorouracil with oxaliplatin; L-OHP, oxaliplatin; NE, not evaluated; OS, overall survival; PFS, progression-free survival; RR, response rate.

Conclusion

In conclusion, L-OHP has been widely used for Japanese AGC patients in clinical practice because of several advantages in terms of toxicity and ease of administration, compared with cisplatin. Depending on the patient's status, combined oral or intravenous 5-FU and adjustment of the L-OHP dose were considered to contribute to a favorable improvement in the prognosis of AGC patients.

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