Second-line chemotherapy for gastric cancer: a new issue lies ahead in global trials

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Abstract Chemotherapy for gastric cancer has been advancing fairly well. It has been indicated that not only advances in first-line chemotherapy but also those in second-line chemotherapy have contributed to the prolongation of overall survival. The Arbeitsgemeinschaft Internistische Onkologie (AIO) study supports the idea that second-line chemotherapy is appropriate in patients with a good general condition. Also, the Japan Clinical Oncology Group (JCOG) integral analysis suggests that advances have been made in second-line chemotherapy. However, most recently reported studies of second-line chemotherapy have been conducted as small-scale phase II or retrospective trials. No randomized control trial to establish standard treatment has been reported. Which regimen is the most appropriate as second-line therapy must be investigated in the future. Currently, molecularly targeted agents for gastric cancer are being developed and tested in global trials. As a new issue in global trials, second-line chemotherapy has been emphasized. In recent global trials, subset analysis showed regional differences in overall survival. This was possibly associated with the regional differences in second-line chemotherapy. When developing new molecularly targeted agents for first-line chemotherapy, we cannot ignore the result that the proportion of patients in whom treatment was switched to second-line chemotherapy was high in Asia. In planning a global trial, this new issue should be sufficiently discussed.

Keywords Gastric cancer · Second-line chemotherapy · Global trial · Molecularly targeted agent

Introduction

Gastric cancer is frequent in Asia, South America, and Eastern Europe, accounting for more than 800,000 new cases per year worldwide, and it is the second most common cause of cancer death [1]. Because early detection strategies are rarely practiced, except in Japan and Korea, most patients will present with advanced-stage disease, and will therefore need palliative chemotherapy. Some chemotherapy regimens have been established as first-line therapy, and some progress has been made in the treatment of advanced-stage disease [2–12]. However, almost all patients with metastatic gastric cancer will develop progressive disease (PD) after first-line therapy. With the availability of several active chemotherapy drugs, many patients who retain a good performance status after the initial treatment remain good candidates for additional therapy.

However, most clinical studies of second-line chemotherapy have been conducted as phase II, small-scale trials. The data obtained are limited, and there is no standard second-line chemotherapy. In this review, differing from previous reviews of second-line chemotherapy [13, 14], I have clarified the significance of second-line chemotherapy based on the recently reported results of randomized control trials of first-line chemotherapy. On the other hand, I refer to the concept of second-line chemotherapy as a potentially confounding factor in recent global trials.

Evidence for second-line chemotherapy

Chemotherapy for advanced/recurrent gastric cancer has been advancing fairly well. As evidence, the median survival in recent randomized comparative studies involving

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patients with advanced/recurrent gastric cancer was markedly longer than that in previous studies [2–12]. It was indicated that not only advances in first-line chemotherapy but also advances in second-line chemotherapy contributed to the prolongation of survival. However, no phase III study has verified the significance of second-line chemotherapy. The results of the Arbeitsgemeinschaft Internistische Onkologie (AIO) comparative study suggest its significance; this study was reported at the 2009 annual meeting of the American Society of Clinical Oncology (ASCO) [15]. In this study, patients in whom first-line therapy led to progressive disease were divided into 2 groups: best supportive care (BSC) and irinotecan groups, to evaluate the usefulness of irinotecan in second-line therapy. In regard to the statistical background, 60 patients per group (2 groups: 120 patients) were required, assuming that irinotecan administration may prolong the median survival time (MST) from 2.5 to 4 months, with an α error (paired) of 5% and a detection power of 80%. However, case registration was insufficient, and the clinical study was completed when 40 patients were enrolled in each of the two groups. The results of analysis were reported. In the irinotecan group, the response rate was 0%. However, the stable disease rate was 58%, and improvement of tumor-related symptoms was achieved in 44% of the patients. In addition, the MSTs in the irinotecan and BSC groups were 123 and 76 days, respectively. Statistically, the overall survival (OS) was longer in the irinotecan group ($p = 0.0027$). These results support the idea that second-line chemotherapy is appropriate in patients with a good general condition. However, which regimen is the most appropriate as second-line therapy must be investigated in the future.

Significance of second-line chemotherapy with respect to randomized comparative studies in Japan

The JCOG 9205 study was started by the Japan Clinical Oncology Group (JCOG) in 1992. Initially, 3 groups, 5-fluorouracil (5-FU), 5-FU + cisplatin, and uracil and tegafur (UFT) + mitomycin C (MMC) groups, were compared [4]. However, the mid-analysis results suggested that UFT + MMC therapy may be less potent than 5-FU therapy. After mid-analysis, the UFT + MMC group was excluded from the subject cohort. Finally, in this study, the results were compared between the 5-FU and 5-FU + cisplatin groups. The OS in the 5-FU + cisplatin group did not exceed that in the 5-FU group. The MST for monotherapy with 5-FU was 7.1 months, and the median progression-free survival (PFS) was 1.9 months. In the JCOG 9912 study, which was conducted subsequently, monotherapy with 5-FU was additionally employed as a

control regimen [10]. The MST for monotherapy with 5-FU was 10.8 months, and the median PFS was 2.9 months. Survival data regarding monotherapy with 5-FU, involving different time-related background factors, were obtained in the two randomized comparative studies conducted by the same clinical study group (Table 1). The JCOG performed integral analysis regarding the two studies, focusing on second-line chemotherapy, and reported the results at the ASCO 2010 meeting [16]. To harmonize the inclusion criteria in the two studies, patients with intestinal stenosis in the JCOG 9205 study and those with adjuvant chemotherapy in the JCOG 9912 study were excluded. Overall survival, time to treatment failure (TTF), and OS minus TTF (OS–TTF) were compared after adjusting for baseline factors using the Cox proportional hazard model. Interestingly, the MST after second-line therapy in the 5-FU group was longer in the JCOG 9912 study.

There are two reasons for the above finding: firstly, the number of effective agents available for second-line therapy in the JCOG 9912 study was larger than the number available at the time of the JCOG 9205 study. In the JCOG 9205 study, early-generation drugs such as cisplatin and MMC were used for second-line therapy. On the other hand, in the JCOG 9912 study, newer drugs such as a taxane and irinotecan were primarily employed for second-line therapy; irinotecan- or taxane-containing regimens were selected in 9% (8/94) of the subjects in the JCOG 9205 study and in 67% (157/233) in the JCOG 9912 study. The difference in treatment options for second-line chemotherapy may have contributed to an MST difference of 3.7 months. On the other hand, the proportion of patients in the 5-FU group in whom treatment was switched to second-line chemotherapy should be compared between the two studies. In approximately 52% of patients receiving 5-FU alone in the JCOG 9205 study, treatment was switched to second-line chemotherapy. In the JCOG 9912 study, the percentage was approximately 83%, showing a 31% increase. This difference may also have led to the MST difference of 3.7 months. Even after adjusting for baseline factors, TTF was similar in the two studies; however, both OS and OS–TTF were longer in the JCOG 9912 study than in the JCOG 9205 study. It was concluded

Table 1 Differences of efficacy profiles and second-line treatment in the 5-fluorouracil arms between the JCOG 9205 and JCOG 9912 trials

	ORR (%)	PFS (months)	MST (months)	Second-line treatment (%)
JCOG 9205 trial [4]	9	1.9	7.1	52
JCOG 9912 trial [10]	11	2.9	10.8	83

JCOG Japan Clinical Oncology Group, ORR overall response rate, PFS progression-free survival, MST median survival time

that survival after treatment failure of 5-FU alone was longer in the JCOG 9912 study even when some potential confounding factors were adjusted for. The results of this combined analysis suggest that advances have been made in second-line chemotherapy and support the use of second-line chemotherapy for gastric cancer. Physicians likely play a key role in whether or not patients receive second-line chemotherapy. Unfortunately, we currently have little evidence to guide treatment. I recommend that patients and physicians earnestly discuss the risks and benefits of second-line chemotherapy using the current best evidence on tolerability and effectiveness.

Regional differences in second-line chemotherapy and new issues in global trials

Trials of the same regimen, S-1 plus cisplatin, were conducted in Japan and other countries. When comparing the SPIRITS trial (S-1 vs. S-1 plus cisplatin), which was carried out in Japan, with the FLAGS trial (5-FU plus cisplatin vs. S-1 plus cisplatin), which was conducted as a global study, there was a regional difference in second-line chemotherapy; there was a marked difference in the proportion of patients in whom treatment was switched to second-line chemotherapy between the two trials [9, 11]. The proportion of patients in whom treatment was switched to second-line chemotherapy was 73% in the SPIRITS study in Japan, whereas it was only 31% in the FLAGS trial. Such a low percentage was also common in other recently reported global studies. The second-line chemotherapy rates ranged from 70 to 83% in studies conducted in Japan, including the JCOG 9912 study [10–12], whereas the rate was only 15% in the REAL-2 trial involving the United Kingdom [7]. As a background factor, we must consider that the insurance coverage systems in Japan and other countries differ markedly. In particular, health insurance in the United Kingdom does not cover second-line chemotherapy; therefore, first-line chemotherapy is very important. The median survival in a phase III study recently reported in Japan was 2–3 months longer than that reported in Europe and the United States [7–12]. This finding may be associated with the difference in the proportion of patients in whom treatment was switched to second-line chemotherapy.

Currently, molecularly targeted agents for gastric cancer are being developed primarily in Japan and Korea and are being tested in global trials. As a new issue in these global trials, second-line chemotherapy has been emphasized. The ToGA study, in which Japanese and Korean patients accounted for more than 50% of the subjects, investigated the efficacy of first-line chemotherapy with trastuzumab in human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer patients; 584 patients meeting

eligibility criteria were randomly assigned to receive 5-FU or capecitabine + cisplatin (FC group: $n = 290$), or 5-FU or capecitabine + cisplatin + trastuzumab (FC + T group: $n = 294$) therapies. The median survival in the FC + T group (13.8 months) was significantly longer than that in the FC group (11.1 months) ($p = 0.0046$), suggesting the usefulness of trastuzumab in HER2-positive gastric cancer patients [17]. In this study, subset analysis showed regional differences in survival; trastuzumab did not influence survival in Asia, but markedly influenced survival in South America. This finding was possibly related to regional differences in second-line chemotherapy, as described above. Approximately 50% of the subjects consisted of Korean and Japanese patients. In these two countries, second-line chemotherapy is positively performed in clinical practice. On the other hand, in South America, second-line chemotherapy is rarely performed. Therefore, the influence of first-line chemotherapy; that is, that of trastuzumab, may have been more marked in South America.

Similarly, in the AVAGAST trial reported at the ASCO 2010 meeting, there were also differences in the proportions of patients in whom treatment was switched to second-line chemotherapy [18]. In that study, there was no influence of bevacizumab on survival in Asia, similar to the lack of influence of trastuzumab in the ToGA trial. In Pan-America, bevacizumab markedly influenced survival. This finding was possibly associated with regional differences in second-line chemotherapy (Table 2). In Asia, the proportion of patients in whom treatment was switched to second-line chemotherapy was high, 66%, whereas the values were 31 and 21% in Europe and Pan-America involving South America, respectively. Briefly, the influence of first-line chemotherapy on survival may be very marked in areas other than Asia. However, when many Japanese/Korean patients are registered, survival after second-line chemotherapy may be prolonged; therefore, there may be no significant difference in the OS. In the future, when developing molecularly targeted agents for first-line chemotherapy, we cannot ignore that there are regional differences in second-line chemotherapy. In planning global trials in the future, this issue should be sufficiently discussed.

Table 2 Proportions of patients receiving second-line chemotherapy by region in the AVAGAST trial [18]

Region	Patients entered (n)	Patients receiving second-line treatment (n)	%
Asia	376	248	66
Europe	249	78	31
Pan-America	149	32	21

Present status and future directions of second-line chemotherapy

Most recently reported studies of second-line chemotherapy consist of small-scale phase II or retrospective trials [19–33]. No randomized control trial to establish standard treatment has been conducted. In clinical practice, irinotecan, docetaxel, or paclitaxel is selected in most patients. However, the effects of monotherapy are limited [20–25]. Various combination therapies have been investigated in small-scale, phase II studies [26–33]. However, according to the results of some recent studies, the response rates ranged from approximately 10 to 20%, and PFS ranged from 2.5 to 4.0 months. There may be no marked differences among these combination therapies (Table 3). One study reported a median survival of 12 months. However, this may have depended on patient selection. As of now, that is all the information we can share. At the time of this writing, I think monotherapy is a reasonable option as a second-line treatment, and combination strategies should be used as a fall-back position. In Japan, weekly paclitaxel is widely used as the second-line chemotherapy in daily clinical practice. On the other hand, the AIO comparative study supported the use of irinotecan for second-line chemotherapy [15]. Much debate has focused on whether irinotecan or weekly paclitaxel is the better second-line agent. Among randomized control trials of second-line chemotherapy that are being conducted, “a randomized phase III study of irinotecan versus weekly paclitaxel in unresectable or recurrent gastric cancer refractory to

combination therapy of fluorouracil plus platinum (WJOG 4007G)”, has been carried out by the West Japan Oncology Group (WJOG). In this study, the primary endpoint was overall survival. Secondary endpoints were PFS, adverse events, and the response rate in patients with target lesions. The sample size was 220 in total, which allowed for the detection of irinotecan superiority over weekly paclitaxel in terms of OS. Final analysis will be performed in 2011. These study results are very important. It should be clarified which of the two agents, irinotecan or paclitaxel, is appropriate as a biologic, platform agent for second-line chemotherapy, and whether the effects of the two agents are similar.

Currently, several second-line or subsequent molecularly targeted agents are being developed and tested in global studies (Table 4). A randomized control trial of lapatinib involving HER2-positive gastric cancer patients (TYTAN trial) is being conducted (weekly paclitaxel vs. weekly paclitaxel + lapatinib). Furthermore, a randomized control trial of a mammalian target of rapamycin (mTOR) inhibitor, everolimus, for BSC is being performed in patients receiving second- and third-line therapies (GRANITE-1 trial) [34]. For new drug development, global trials are also necessary in the future. However, in randomized control trials in which OS is established as the primary endpoint of first-line chemotherapy, it is difficult to detect a difference unless molecularly targeted agents with a clear target, such as trastuzumab, are employed; this difficulty arises because there are regional differences in second-line chemotherapy. In particular, Japan and Korea,

Table 3 Efficacy profiles of combination chemotherapy in the second-line setting

	Regimen	ORR (%)	PFS (months)	MST (months)	Reference number
	Paclitaxel/doxifluridine	18.2	4.0	10.7	[26]
	Paclitaxel/capecitabine	34.6	4.5	7.5	[27]
	Docetaxel/doxifluridine	18.8	2.6	12.7	[28]
	Docetaxel/irinotecan	20.4	2.7	8.9	[29]
	Docetaxel/oxaliplatin	10.5	4.0	8.1	[30]
ORR overall response rate, PFS progression-free survival, MST median survival time, NE not evaluated	Irinotecan/5-fluorouracil	18.2	2.3	5.1	[31]
	Irinotecan/capecitabine	17.0	3.1	6.5	[32]
	Methotrexate/5-fluorouracil	9.0	NE	7.9	[33]

Table 4 Phase III studies of targeted agents for second-line treatment in advanced gastric cancer

Agent	Target	Chemotherapy partner	N	Endpoint	Status
Lapatinib	HER2 EGFR	Paclitaxel	260	OS	Ongoing
Ramucirumab	VEGFR-2	Paclitaxel	663	OS	Ongoing
Everolimus	mTOR	None	442	OS	Ongoing

OS overall survival, mTOR mammalian target of rapamycin, HER2 human epidermal growth factor receptor 2, EGFR epidermal growth factor receptor, VEGFR-2 vascular endothelial growth factor receptor 2

where second-line chemotherapy is actively performed, play a principal role in registration. For the future development of molecularly targeted agents, it might be necessary to discuss the adoption of PFS as the primary endpoint.

Conclusions

At this time, no standard second-line chemotherapy has clearly emerged in gastric cancer treatment, and none of the new molecularly targeted agents under investigation has been identified as being appreciably useful for second-line-chemotherapy. Given the lack of solid evidence, it is too early to know whether a number of novel regimens will ultimately achieve traction as useful standard second-line chemotherapies. New evidence and new drugs are needed to make the necessary further improvements in the management of gastric cancer. In global trials, however, we have learned of the difficulties in selecting survival benefit as the primary endpoint, with these difficulties arising because of the regional differences in the management of this disease. In planning global trials, this new issue should be sufficiently discussed.

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