Future Perspectives for the Development of Chemotherapy for Advanced Gastric Cancer: Japanese and Global Status

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Introduction

In 2008, gastric cancer was the fourth most common malignancy (989,000 cases, 7.8% of all cancers) in the world, coming after cancers of the lung, breast and colorectum. Gastric cancer is the second leading cause of death from cancer in both sexes worldwide (738,000 deaths, 9.7% of all cancers), with the highest mortality in eastern Asia (28.1 per 100,000 in men, 13.0 per 100,000 in women) and the lowest in North America (2.8 and 1.5, respectively) [1]. In Japan, gastric cancer is the most commonly diagnosed cancer and second after lung cancer as a leading cause of cancer-related mortality.

Standard chemotherapeutic regimens for advanced gastric cancer (AGC) differ between western countries and Japan because of several factors, including historical differences in previous randomized trials, differences in health insurance systems among countries and in the approval status of new drugs. In Japan, standard regimens for chemotherapy remained controversial until 2007, when the results of several large randomized phase III studies were reported [2, 3], establishing S-1 plus cisplatin (CS) as the standard treatment for AGC. In addition, global randomized studies have demonstrated that...
trastuzumab enhances the response to chemotherapy in patients with human epidermal growth factor receptor 2 (HER2)-positive AGC [4]. In this article, we review recent advances in chemotherapy for gastric cancer in Japan and the rest of the world and discuss future perspectives.

Recent Progress in Chemotherapy for AGC: Global Status

V-325 Study (table 1)

Despite previous randomized studies, standard regimens for the chemotherapy of AGC remained controversial [5–7]. In 2005, the final results of the V-325 study were presented at the annual meeting of the American Society of Clinical Oncology (ASCO) [8]. This study used a CF regimen [cisplatin 100 mg/m² on day 1 plus 5-fluorouracil (5-FU) 1,000 mg/m²/day as a continuous infusion on days 1–5, every 4 weeks] as the reference arm. The results of previous randomized studies showed that CF did not significantly prolong overall survival (OS) when compared with other regimens, but had a high overall response rate (ORR) and a long time to progression. Consequently, CF has been widely used clinically in Western countries.

The V-325 trial randomly assigned 457 chemotherapy-naive patients with AGC to receive DCF (docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1, plus 5-FU 750 mg/m²/day as a continuous infusion on days 1–5, every 3 weeks) or CF. ORR, time to progression, and median survival time (MST) were significantly better with DCF (37%, 5.6 and 9.2 months, respectively) than with CF (25%, 3.7 and 8.6 months, respectively). Grade 3/4 treatment-related adverse events occurred more frequently with DCF than with CF (81 vs. 75%), and neutropenia was more frequent with DCF than with CF (82 vs. 57%). The authors concluded that docetaxel combined with CF and appropriate risk management is a new treatment option for advanced gastric cancer. At present, modifications of DCF are being studied in an attempt to reduce toxicity, improve safety and enhance the ability to administer it without interruption [9].

REAL 2 Study (table 1)

The REAL 2 study used a two-by-two design to evaluate several modifications of the ECF (epirubicin/
cisplatin/5-FU) regimen, including the substitution of capecitabine for 5-FU and oxaliplatin for cisplatin [10]. The primary end point was to demonstrate noninferiority in OS for capecitabine compared to 5-FU, and for oxaliplatin compared to cisplatin. A total of 1,002 chemotherapy-naïve patients with histologically confirmed adenocarcinoma, squamous carcinoma, or undifferentiated carcinoma of the esophagus, esophagogastric junction, or stomach were randomly assigned to receive one of four regimens: ECF, EOF (epirubicin/oxaliplatin/5-FU), ECX (epirubicin/cisplatin/capecitabine), or EOX (epirubicin/oxaliplatin/capecitabine). The median survival times for the 5-FU regimens (ECF and EOF), the capecitabine regimens (ECX and EOX), the cisplatin regimens (ECF and ECX), and the oxaliplatin regimens (EOX and EOF) were 9.6, 10.9, 10.1 and 10.4 months, respectively. The results met predefined noninferiority criteria for both comparisons, i.e. capecitabine was noninferior to 5-FU and oxaliplatin was noninferior to cisplatin. A secondary analysis showed that OS was longer with EOX than with ECF, with a hazard ratio (HR) for death of 0.80 in the EOX group (95% CI, 0.66–0.97; p = 0.02).

**ML17032 Trial** (table 1)

Another multinational randomized phase III trial compared cisplatin plus capecitabine (CX) with CF [11]. The primary end point was to demonstrate noninferiority in progression-free survival (PFS). A total of 316 chemotherapy-naïve patients with previously untreated measurable AGC were enrolled in Asia, Latin America, and eastern European countries and randomly assigned to either CX or CF. The median PFS, which was 5.6 months for CX and 5.0 months for CF, satisfied predefined criteria for noninferiority. The MST was 10.5 months for CX and 9.3 months for CF. The most common treatment-related adverse events generally occurred at similar rates in both treatment arms. However, hand-foot syndrome was more frequent with CX than with CF (22 vs. 4%), whereas vomiting (59 vs. 49%) and stomatitis (26 vs. 12%) were more common with CF. The authors concluded that capecitabine can replace infused 5-FU for the treatment of AGC and proposed that CX should be a new standard treatment option for AGC.

**FLAGS Trial** (table 1)

The ASCO Gastrointestinal Cancers Symposium 2009 reported the results of the FLAGS (First-Line Advanced Gastric Cancer Study) trial, which compared CS with CF [12]. This study was conducted at 146 centers in 24 countries. A total of 1,053 patients were randomly assigned to receive either CS (S-1 50 mg/m² orally for 21 days and cisplatin 75 mg/m² intravenously on day 1, repeated every 4 weeks) or CF. The primary end point was superiority in OS with CS compared to CF in patients with advanced, untreated gastric or gastroesophageal adenocarcinoma. The median OS was 8.6 months in the CS group and 7.9 months in the CF group (HR, 0.92; 95% CI, 0.80–1.05; p = 0.20). The median PFS was 4.8 months in the CS group and 5.6 months in the CF group (HR, 0.99; 95% CI, 0.86–1.14; p = 0.92), and the ORR was 29.1 versus 31.9%, respectively. None of these variables differed significantly between the groups. Significant safety advantages were obtained in the CS group when compared with the CF group for the rates of grade 3/4 neutropenia (32.3 vs. 63.6%), complicated neutropenia (5.0 vs. 14.4%), stomatitis (1.3 vs. 13.6%), hypokalemia (3.6 vs. 10.8%), and treatment-related deaths (2.5 vs. 4.9%). The authors concluded that CS did not prolong the OS of patients with advanced gastric or gastroesophageal adenocarcinoma when compared with CF, but that it did result in a significantly improved safety profile. The results of noninferiority analysis of OS with CS versus CF and the results of additional subset analyses according to histological type were also reported at ASCO 2009. The noninferiority margin was decided on the basis of the results of previous studies and meta-analyses, and an HR of 1.10 was considered appropriate. Therefore, if the upper limit of the HR in this study was less than 1.10, noninferiority was considered to have been significantly demonstrated. On subgroup analysis according to histological type, the subset of patients with diffuse type tumors had significantly better outcomes in the CS group (HR, 0.83; p = 0.04). The speakers concluded that CS was optimally suited to replace CF and that additional studies designed to confirm the high effectiveness of CS in patients with diffuse type tumors were warranted.

**ToGA Trial** (table 1)

The results of the ToGA (Total Gene Expression Analysis) trial of trastuzumab, a monoclonal antibody against HER2, plus standard chemotherapy in patients with HER2-positive AGC were also reported at ASCO 2009 [4]. This was the first phase III study of a molecular target agent to be performed in the field of gastric cancer. In this study, patients with unresectable, recurrent, HER2-positive gastric cancer were randomly assigned to the control group and given either CF or CX, or to the trastuzumab group and given trastuzumab in addition to either CF or CX. The primary end point was superior OS in the trastuzumab group. HER2 screening was done by immunohis-
to chemotherapy (IHC) and fluorescence in situ hybridization (FISH) at a central laboratory. Patients whose tumors were IHC3+ or FISH-positive were eligible. HER2 screening was performed in a total of 3,807 patients, and 810 patients (22.1%) were HER2-positive, among whom 584 were finally enrolled. A total of 24 countries participated, and 55% of the patients were enrolled in Asia (including Japan), 33% in Europe, 9% in Central and South America and 3% in other countries. Of the enrolled patients, 18% had cancer of the esophagogastric junction, and 75% had a histological diagnosis of intestinal type. Analysis of the primary end point of OS showed that MST was 11.1 months in the control group compared to 13.8 months in the trastuzumab group (HR, 0.74; 95% CI, 0.60–0.91; p = 0.0046). Trastuzumab was thus demonstrated to prolong survival significantly. The median PFS (5.5 vs. 6.7 months; HR, 0.71; p = 0.0002) and ORR (34.5 vs. 47.3%; p = 0.0017) were also significantly better in the trastuzumab group than in the control group. On subset analysis according to HER2 expression level, the difference in MST was particularly remarkable in patients with IHC2+/FISH-positive or ICH3+ tumors (n = 446), with an MST of 11.8 months in the control group versus 16.0 months in the trastuzumab group (HR, 0.65; 95% CI, 0.51–0.83). Toxicity did not differ between the groups. The authors concluded that trastuzumab plus chemotherapy was an important treatment option for HER2-positive AGC.

The ToGA trial was the first study to demonstrate the effectiveness of molecular target therapy for gastric cancer. These results are considered to represent a breakthrough in the treatment of gastric cancer and may lead to the establishment of independent subgroups of HER2-positive patients, similar to breast cancer. It is now necessary to standardize criteria for the histopathological diagnosis of HER2-positive tumors. Following the success of trastuzumab in breast cancer, the results of the ToGA trial will most likely accelerate the development of personalized therapy.

**AVAGAST Trial** (table 1)

The results of the AVAGAST trial demonstrating the efficacy of bevacizumab, a monoclonal antibody against vascular endothelial growth factor, in patients with AGC were reported at ASCO 2010 [13]. This randomized, double-blind, placebo-controlled, phase III clinical trial was a global study performed primarily in Japan and South Korea. Patients with unresectable, previously untreated gastric cancer were randomly assigned to receive CX plus bevacizumab or CX plus a placebo. Patients received CX plus an intravenous infusion of bevacizumab 7.5 mg/kg or a placebo on day 1 of a 3-week cycle. The primary end point was OS. The secondary end points included PFS, time to progression, ORR, duration of response, safety, quality of life and biomarker levels. A total of 774 patients were registered at 93 centers in 17 countries. More than 40% of the study group was enrolled in Japan and South Korea.

As for OS, MST was 10.1 months in the placebo group versus 12.1 months in the bevacizumab group (HR, 0.87; p = 0.10); this difference was not significant. However, median PFS was 5.3 months in the placebo group versus 6.7 months in the bevacizumab group (HR, 0.80, p = 0.0037), and the ORR was 37% in the placebo group versus 46% in the bevacizumab group (p = 0.032), indicating significantly better results for these variables in patients who additionally received bevacizumab. On subgroup analyses of OS according to geographic region, MST did not differ significantly between the treatment groups in Asia (placebo vs. bevacizumab group, 12.1 vs. 13.9 months; HR, 0.9) or Europe (8.6 vs. 11.1 months; HR, 0.85), but was significantly better in the bevacizumab group in America (6.8 vs. 11.5 months; HR, 0.63). A subgroup analysis of PFS according to geographic region showed that PFS did not differ between the treatment groups in Asia (placebo vs. bevacizumab group, 5.6 vs. 6.7 months; HR, 0.92), but was significantly longer in the bevacizumab group in Europe (4.4 vs. 6.9 months; HR, 0.71) and America (4.4 vs. 5.9 months; HR, 0.65). The proportion of patients who went on to receive second-line therapy were 66% in Asia, 31% in Europe, and 21% in America. The safety of bevacizumab was consistent with the results of previous studies in other types of cancer: bevacizumab did not potentiate the toxicity of CX. The results of the AVAGAST trial were negative and highlighted the difficulties involved in performing a global study. The results of biomarker analysis are scheduled to be reported in the future.

**Recent Progress in Chemotherapy for AGC: Japanese Status**

**JCOG 9912 Trial** (table 2)

In the 1990s, a large randomized phase III trial, JCOG (Japan Clinical Oncology Group) 9205, was conducted to compare 5-FU alone with CF and with uracil-tegafur plus mitomycin C in patients with unresectable AGC [14]. Although CF achieved a better response rate (RR) and PFS than 5-FU monotherapy, there was no difference in OS...
between these 2 arms (7.3 and 7.1 months for CF and 5-FU, respectively). Because of its better safety, 5-FU monotherapy remained as a reference arm in the next 3-arm, randomized, phase III trial, JCOG 9912. This trial was conducted to evaluate whether cisplatin plus irinotecan treatment was superior to and S-1 was noninferior to the reference arm 5-FU [2]. The MSTs achieved by 5-FU, cisplatin plus irinotecan and S-1 were 10.8, 12.3 and 11.4 months, respectively. Survival was not significantly better with cisplatin plus irinotecan than with 5-FU (p = 0.055); however, the noninferiority of S-1 versus 5-FU was confirmed (p < 0.001).

**SPIRITS Trial** (table 2)

S-1 was then widely used in Japan as first-line chemotherapy for AGC. Because promising results were obtained in phase II studies of S-1-based combination therapy, three large randomized phase III studies, the SPIRITS trial, the TOP-002 trial and the JACCRO GC03 trial, were conducted independently to compare S-1 monotherapy with S-1-based combined regimens.

In the SPIRITS trial, 305 chemotherapy-naïve patients with AGC were randomly assigned to receive either CS (S-1 80 mg/m² orally for 21 days and cisplatin 60 mg/m² intravenously on day 8, repeated every 35 days) or S-1 alone (S-1 80 mg/m² orally for 28 days, followed by a 14-day rest, repeated every 42 days) [3]. The primary end point was OS, and the secondary end points were PFS, ORR and safety. Median OS was significantly longer in the S-1 group than in the S-1-alone group (13.0 vs. 11.0 months; HR, 0.77; 95% CI, 0.61–0.98; p = 0.04). The median PFS was significantly longer in the S-1 group than in the S-1-alone group (6.0 vs. 4.0 months; p < 0.0001) and the ORR was significantly higher in the S-1 group than in the S-1-alone group (54 vs. 31%; p = 0.002). Grade 3 or 4 adverse events, including leukopenia, neutropenia, anemia, nausea and anorexia, occurred more frequently in the S-1 group than in the S-1-alone group. There were no treatment-related deaths in either group. On the basis of these results, S-1 became a new standard first-line treatment for AGC in Japan.

**Other Phase III Trials** (table 2)

A randomized phase III trial, TOP-002, was conducted to evaluate the efficacy and safety of S-1 plus irinotecan (IRIS) compared to S-1 alone for AGC [15]. Previously untreated patients were randomly assigned to receive S-1 alone or IRIS (S-1 80 mg/m² orally for 21 days and irinotecan, 80 mg/m² intravenously on days 1 and 15, every 5 weeks). The primary end point was OS.

### Table 2. Recent Japanese phase III trials in AGC

<table>
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<th>Trial</th>
<th>Regimen</th>
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<th>RR</th>
<th>PFS</th>
<th>p value</th>
<th>MST</th>
<th>p value</th>
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<td>JCOG 9912 [2]</td>
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<td>2.9</td>
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<tr>
<td></td>
<td>CPT-11 + cisplatin</td>
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<td>&lt;0.0001</td>
<td>12.3</td>
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<td>SPIRITS [3]</td>
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<td>4.0</td>
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<td>S-1 + cisplatin</td>
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<td></td>
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<td>NS</td>
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<td>ISO-5FU10 [16]</td>
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CPT-11 = Irinotecan; MMC = mitomycin C; UFT = tegafur-uracil.
¹ For noninferiority to 5-FU.
² Time to treatment failure.
the MST was 12.8 months in the IRIS group compared to 10.5 months in the S-1-alone group. IRIS was not significantly superior to S-1 alone (p = 0.23).

A phase III trial designed to investigate the noninferiority of 5-FU combined with L-leucovorin (RPMI) compared to S-1 alone in patients with AGC was reported in 2009 [16]. The primary end point was OS. RPMI (L-leucovorin 250 mg/m^2 as a 2-hour intravenous infusion plus 5-FU as a 600-mg/m^2 intravenous bolus) was given intravenously 6 times weekly followed by a 2-week rest period, within an 8-week cycle. A total of 191 chemotherapy-naive patients were randomly assigned to the RPMI group or the S-1 group. MST was 10.3 months in the RPMI group and 8.3 months in the S-1 group, and the HR of RPMI relative to S-1 was 0.84 (95% CI, 0.60–1.18). Median PFS was 4.0 months in the RPMI group and 3.5 months in the S-1 arm group (HR, 0.76; 95% CI, 0.55–1.06). There were no significant differences in safety or quality of life between the two groups. RPMI was significantly noninferior to S-1 with respect to OS and PFS in the first-line treatment of AGC. RPMI is an effective alternative to S-1, particularly in patients in whom oral intake is precluded by AGC.

In the JACCRO GC03 trial, a randomized phase III study, patients were enrolled in Japan and Korea and randomly assigned to receive 3-week cycles of docetaxel 40 mg/m^2 intravenously on day 1 and S-1 80 mg/m^2 orally for 2 weeks, or 6-week cycles of S-1 alone [17]. The primary end point was the superiority of OS with docetaxel plus S-1 compared to S-1 alone in patients with previously untreated AGC. MST was 11.0 months in the S-1 alone group versus 12.8 months in the b docetaxel plus S-1 group (HR, 0.88; p = 0.14); this difference was not significant.

### Future Perspectives

#### Ongoing Phase III Studies of First-Line Chemotherapy for AGC in Japan

Oxaliplatin is not approved for the indication of gastric cancer in Japan. Because good results were obtained with S-1 plus oxaliplatin in a phase II study [18], a randomized phase III study is currently in progress to demonstrate the noninferiority of S-1 plus oxaliplatin to CS and thereby obtain approval of oxaliplatin for the indication of gastric cancer. The target number of patients is 600, and the primary end points are PFS and OS.

#### Triple-Drug Regimens in Japan

In Europe and North America, triple-drug regimens such as ECF and DCF are widely used as first-line chemotherapy. In Japan, CS has become a standard regimen for chemotherapy. However, triple-drug therapy with docetaxel/cisplatin/S-1 is expected to become the next candidate for a standard regimen. Two phase II studies of docetaxel/cisplatin/S-1 performed in Japan have been reported [19, 20]. In the KDOG 0601 study, Nakayama et al. [20] used a combination of docetaxel 40 mg/m^2 and cisplatin 60 mg/m^2 intravenously on day 1, and S-1 80 mg/m^2 orally for 2 weeks, given every 4 weeks (KDOG regimen). The ORR was 81.3% and the median PFS was 8.7 months. Because the KDOG regimen is very effective and well tolerated, it has been used in studies of neoadjuvant chemotherapy in patients with resectable disease. It is also being considered as a regimen for randomized studies in patients with unresectable disease.

#### Molecular Target Agents

Phase III studies of panitumumab, cetuximab, lapatinib, and everolimus (RAD001), in which Japan is playing a major role, are now ongoing in patients with AGC.
(table 3). The REAL-3 trial is being performed in the UK to examine whether panitumumab, the first fully human monoclonal antibody against epidermal growth factor receptor, enhances the therapeutic value of first-line treatment with CX. The EXPAND study is a global ongoing trial evaluating the benefits of adding cetuximab, a human-murine chimeric monoclonal antibody against epidermal growth factor receptor, to first-line treatment with CX. In another controlled study, the HER1/2 dual inhibitor lapatinib is being combined with capecitabine plus oxaliplatin for first-line treatment (LOGiC trial) and with paclitaxel for second-line treatment. In patients with HER2-positive gastric cancer, therapeutic strategies similar to those for breast cancer are expected to be pursued. Double-blind, randomized studies comparing everolimus (RAD001), an oral inhibitor of the mammalian target of rapamycin (mTOR), with placebo for second- and third-line treatment are now in progress. Various phase II studies of the multiple tyrosine kinase inhibitors TSU68 and sorafenib, nimotuzumab (a humanized IgG1 monoclonal antibody targeting epidermal growth factor receptor), and other agents are ongoing, and the results are eagerly awaited.

**Personalized Therapy**

Personalized therapy has become a very important issue with the development of molecular target agents. When compared with other types of cancer, few biomarkers have been reported to be significant predictors of outcomes or response in gastric cancer. Trastuzumab showed a survival benefit in patients with HER2-positive gastric cancer in the ToGA trial. In the near future, trastuzumab is expected to be approved for the indication of gastric cancer, and patients with HER2-positive tumors will most likely receive targeted therapy with trastuzumab. In addition, lapatinib is active against HER2-positive breast cancer after treatment failure with trastuzumab. Lapatinib is being investigated in first and second-line settings for the management of AGC. However, the proportion of HER2-positive tumors is low, about 20%. Investigations of potent biomarkers other than HER2 are urgently needed.

Koizumi et al. [21] immunohistochemically studied the relations of the expressions of thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD) to the response to capecitabine in patients with advanced or recurrent gastric cancer. The RR was significantly higher (p = 0.028) in patients with TP-positive and DPD-negative tumors (RR = 60%) than in the remaining patients (RR = 13%). Trastuzumab combined with CX would be more beneficial in patients whose tumors have high TP expressions and low DPD expression with an HER2-positive tumor gene profile.

The SPIRITS trial showed a survival benefit in patients who received CS compared to S-1 alone for the first-line treatment of AGC. In a retrospective biomarker study, we aimed to develop a methodology to identify patients with AGC who would respond better to S-1 alone than to CS [22]. We studied 120 patients who received S-1 alone or CS as first-line chemotherapy for AGC and quantitatively evaluated mRNA levels of several molecular markers in paraffin-embedded specimens of primary tumors. Multivariate survival analysis of data from patients who received S-1 monotherapy demonstrated that low TP and thymidylate synthase (TS) expression and high orotate phosphoribosyltransferase expression were significant predictors of prolonged OS. In patients with lower expression of both TP and TS than the cutoff values, S-1 alone was associated with longer OS than CS (18.2 vs. 9.4 months), and the overall frequency of adverse events tended to be lower with S-1 alone than with CS. Our results suggested that these biomarkers are useful for the identification of patients with AGC who are likely to benefit from treatment with S-1 alone: those who had tumors with low TP and TS expression had better survival with less toxicity. Others should be given CS as first-line chemotherapy. Future prospective clinical and pharmacogenomic studies should confirm the usefulness of the biomarkers identified in retrospective studies.

**Second-Line Chemotherapy**

The results of a randomized study comparing irinotecan alone with best supportive care (BSC) for second-line treatment in gastric cancer was reported by the Arbeitsgemeinschaft Internistische Onkologie group at ASCO 2009 [23]. The target number of patients was 120, but the study was terminated after the enrollment of 40 patients because of poor accrual. The primary end point was OS. MST was 73 days in the BSC group compared to 123 days in the irinotecan group (HR, 0.48; 95% CI, 0.25–0.92; p = 0.023). Irinotecan was thus shown to significantly prolong survival. This study had several problems, such as the poor enrollment, but deserves attention because it was the first controlled study to demonstrate the value of second-line chemotherapy and irinotecan compared to BSC for patients with gastric cancer.

In Japan, weekly paclitaxel, irinotecan alone, or cisplatin/irinotecan is widely used as second-line chemothera-
apy, but a standard regimen for patients with AGC who do not respond to first-line chemotherapy is yet to be established. Several phase III studies are ongoing to compare these regimens.

Conclusions

Many randomized trials of various regimens for chemotherapy have been conducted, and the clinical outcomes of patients with AGC have improved. In Europe and North America, CX, ECF, and DCF are primarily used as standard therapy for AGC, where CS is standard in Japan. Capecitabine had not been approved for the treatment of gastric cancer in Japan. Therefore, S-1, developed in Japan, has mainly served as a base drug for the development of regimens for combination chemotherapy. Recently, Japan has participated in global studies evaluating the potential benefits of combining molecular targeting agents with CX. Then capecitabine and trastuzumab were approved recently. As for triple-drug therapy, a phase II study of docetaxel/cisplatin/S-1 has been completed. Studies evaluating the effectiveness of triple-drug therapy for neoadjuvant chemotherapy and controlled studies comparing such therapy with CS in patients with unresectable gastric cancer are planned.

Recently, new drug development has focused on molecular target agents, and personalized therapy for AGC has just begun. In patients with HER2-positive AGC, trastuzumab showed a survival benefit when combined with chemotherapy. Furthermore, abundant information about the heterogeneity and the biological backgrounds of AGC patients has been compiled. New strategies for the development of personalized therapy should be studied in the future.

References


