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Recent Advances in Chemotherapy for Advanced Gastric Cancer in Japan

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Abstract
In the early 1990s, a combination of 5-fluorouracil (5-FU) and cisplatin was widely adopted to treat advanced gastric cancer; however, no survival advantage over single-agent 5-FU was confirmed by the results of randomized trials conducted over a long period. Recently developed agents such as irinotecan, taxanes (docetaxel), and new oral fluorouracil (S-1) have yielded more promising results, with a response rate of over 50% and a median survival time of over 10 months in combination studies. These newer combination regimens were investigated in various randomized phase III studies to clarify if the newer-generation regimens provided a survival advantage over the older-generation regimens. Based on the findings of a large randomized study, S-1 has become standard in the adjuvant setting after D2 dissection curatively resected stage II and III gastric cancer. This article reviews the recent advances in gastric cancer chemotherapy, especially in Japan.

Key words Gastric cancer · Chemotherapy · Standard chemotherapy

Introduction

Gastric cancer (GC) is the most common malignancy in Japan. In 1998, more than 100000 new cases were reported[1] and by 2015, it is anticipated that this number will have climbed to nearly 150000.[2] The only potentially curative treatment for GC is surgical resection of all of the gross and microscopic disease; however, recurrence is common, both in regional and distant sites. The standard treatment for advanced or relapsed gastric cancer (AGC) is chemotherapy, aimed at prolonging survival.

Until about 10 years ago, there were few medical oncologists in Japan, and gastrointestinal surgeons played the part of oncologists in designing cancer chemotherapy for patients with gastric or colorectal carcinomas. The educational systems for medical oncologists were initiated by the Japan Society of Medical Oncology (JSMO). However, from 2005 to 2007 only 205 specialists in medical oncology passed the JSMO examination. The JSMO predicts that 80 medical oncologists will be initiated into the system each year, but this will be insufficient to cover all patients who have AGC. Thus, surgeons must continue to treat their patients with AGC oncologically in Japan. Our aim in writing this review is to make surgeons aware of the widely used regimen or standard chemotherapy for GCs, because we expect them to be able to treat their AGC patients effectively and safely.

Anticancer Drugs for AGC

One of the most widely studied single-agent chemotherapies is the antimetabolite, 5-fluorouracil (5-FU), which confers response rates of approximately 20%.[3,4] Tumor antibiotics (mitomycin C, doxorubicin, and epirubicin), heavy metals (cisplatin and carboplatin), taxanes (paclitaxel and docetaxel), and camptothecins (irinotecan and topotecan) have also been evaluated in the treatment of AGC and afford response rates ranging from 5% to 30%.[5–7] Newer fluorinated pyrimidines such as the 5-FU prodrug, UFT (uracil and tegafur), and 5-FU derivatives such as S-1, are of particular interest since they can be administered orally and allow for mimicking of conventional infusional therapy.

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Is Chemotherapy Effective Against AGC?

Several combination chemotherapeutic regimens have been evaluated for their efficacy and tolerability in the treatment of AGC. They often achieve adequate response rates with variable toxicity in previously untreated AGC patients. Compared with the best supportive care, the median survival with combination chemotherapy appears to be increased by 2 months or longer.[8,9]

Standard Chemotherapy for AGC in Western Countries

In Western countries, FAM (5-FU/adriamycin/mitomycin C), FAMTX (5-FU/adriamycin/methotrexate), ELF (etoposide/leucovorin/5-FU), and CF (cisplatin/5-FU) regimens have been compared in several studies. In consideration of their moderate activity, we do not recommend that any of the evaluated regimens be regarded as the standard treatment. In a prospective, randomized phase III study, Waters et al.[10] compared a combination of epirubicin, cisplatin, and 5-FU (ECF) with FAMTX in previously untreated patients with AGC. This ECF regimen resulted in significantly higher response rates (46% vs 21%), median survival (8.7 vs 6.1 months), and 2-year survival rates (14% vs 5%), and is the de facto standard treatment for AGC in Europe.

In a randomized phase III study (TAX325), Moiseyenko et al.[11] compared the efficacy and safety of cisplatin and 5-FU (CF) vs docetaxel, cisplatin, and 5-FU (TCF) as front-line therapy in patients with metastatic or nonresectable AGC. The final analysis revealed that the addition of docetaxel to CF resulted in significantly higher response rates (37% vs 25%, for TCF and CF, respectively). Time-to-progression, the primary study endpoint, was significantly higher in the TCF-treated patients than in the CF-treated patients (5.6 months vs 3.7 months, respectively; $P < 0.0004$). At the time of this interim analysis, the observed difference in median overall survival favored TCF over CF (9.2 vs 8.6 months, respectively; $P = 0.0201$). The common severe toxicities associated with TCF and CF included stomatitis (20.8% and 27.2% of subjects, respectively), lethargy (21.3% and 17.9%), diarrhea (20.4% and 8.0%), nausea (15.8% and 18.8%), vomiting (14.9% and 18.8%), and febrile neutropenia or neutropenic infection (30% and 13.5%). Based on the results of the TAX325 trial, TCF is regarded as standard chemotherapy in the United States.

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Until the early 1990s there was no standard chemotherapy in Japan, although 5-FU infusion, CF, and uracil-tegafur, and mitomycin C (UFTM) regimens were widely employed in the clinical setting. In a three-arm, large randomized phase III trial, Ohtsu et al.[12] compared 5-FU with CF and with UFTM. They found 5-FU to be equal to or better than UFTM in terms of response and survival. Although CF achieved a better response rate and progression-free survival (PFS) than 5-FU monotherapy, there was no difference in overall survival between these two arms (7.3 and 7.1 months for CF and 5-FU, respectively). 5-FU monotherapy remained as a reference arm in the next phase III trial of the JCOG group.

New Anticancer Agents

S-1 consists of a 1:0.4:1 molar ratio mixture of tegafur and two 5-FU-modulating substances: gimeracil (5-chloro-2,4-dihydroxypyrimidine, CDHP) and oteracil (potassium oxonate). Sakata et al.[13] investigated the efficacy of S-1 as a single chemotherapeutic agent in AGC patients in a late phase II study. Four cycles of S-1 were administered twice a day to 51 patients at a dose of 80 mg/m^2 per day. One complete response (CR) and 24 partial responses (PRs) were observed, with an overall response rate of 49%. The median survival time (MST) achieved by S-1 in a phase II study was 8 months and it was generally well tolerated, the major toxicities including anemia, leukopenia, granulocytopenia, diarrhea, malaise, and proteinuria.

Boku et al.[14] reported a phase II trial of cisplatin/CPT-11 combination chemotherapy involving 44 patients with AGC by the JCOG. Cisplatin was administered at a dose of 80 mg/m^2 on day 1, and CPT-11 was administered at a dose of 70 mg/m^2 on days 1 and 15 every 4 weeks. They reported 1 CR and 20 PR, with an overall response rate of 48.0%, and an MST of 9 months. The grade 4 major toxicities with this combination were leukopenia (9.0%), neutropenia (57.0%), thrombocytopenia (2.0%), and anemia (5.0%).

JCOG 9912 Trial

The JCOG conducted another three-arm, randomized phase III trial in 1999 (the JCOG 9912 trial), evaluating the superiority of cisplatin/CPT-11 over the reference arm 5-FU, and the noninferiority of S-1 to 5-FU. The MSTs achieved by 5-FU, cisplatin/CPT-11, and S-1 were 10.8 months, 12.3 months, and 11.4 months,

respectively. Survival was not significantly better with cisplatin/CPT-11 vs 5-FU ($P = 0.055$); however, the non-inferiority of S-1 vs 5-FU was confirmed ($P < 0.001$). Subsequently, S-1 has been widely used in Japan as the standard and first-line chemotherapy for AGC.

Combination Chemotherapy with S-1

The efficacy of combination chemotherapy with S-1 in AGC has been assessed in a number of phase I/II studies. Cisplatin at a dose of 60 mg/m^2 on day 8 was combined with S-1 for 3-weeks-on and 2-weeks-off.[15] Treatment was repeated every 5 weeks, unless disease progression was observed. The subjects of this trial were 19 AGC patients, and the incidences of severe (grade 3/4) hematological and nonhematological toxicities were 15.8% and 26.3%, respectively, but all cases were manageable. The response rate was 74% (14/19; 95% confidence interval, 54.9–90.6), and the MST was 383 days.

Komatsu et al.[16] reported the results of a phase I/II study with CPT-11 and S-1 (IRIS) in AGC patients. S-1 was given orally twice a day for 14 days, and CPT-11 was administered as a 90-min intravenous infusion on days 1 and 15. This regimen was repeated every 4 weeks. Fifteen patients were registered in the phase I study and 9 were added to the phase II study. Most of the nonhematological toxicities were classified as grade 2 or lower, except for grade 3 nausea and grade 3 level 2 dermatitis. The hematological toxicities consisted of grade 4 neutropenia in one patient at level 1 and level 2 in phase I, and grade 4 neutropenia in 4 patients at level 2 in phase II. All of these patients recovered after the drug was suspended. These side effects were tolerable, and the overall response rate was 54.2%. The MST achieved with this regimen was 581 days.

Yoshida et al.[17] performed a phase I study and a phase II study of docetaxel in combination with S-1 in patients with AGC. In the phase I study, neutropenia and leukocytopenia were the dose-limiting toxicities (DLTs). The recommended dose (RD) was 40 mg/m^2 on day 1 for docetaxel and 80 mg/m^2 on days 1–14 for S-1, every 3 weeks. In the phase II study, the response rate was 52.1% and the MST was 434 days. The most common severe toxicities were neutropenia (18.5%), leukopenia (12.3%), anemia (2.6%), stomatitis (10.4%), anorexia (6.3%), and nausea (6.3%). Yamaguchi et al.[18] reported a phase I/II study of docetaxel in combination with S-1. During dose escalation, G3 infection without neutropenia was the DLT. The RD was 40 mg/m^2 on day 1 for docetaxel and 80 mg/m^2 on days 1–14 for S-1, every 4 weeks. The response rate was 45.7%, the MST was 14.2 months, and the PFS was 4.3 months. The most common severe toxicities were neutropenia (67.4%), leukopenia (41.3%), anemia (21.7%), anorexia (21.7%), nausea (6.5%), and stomatitis (6.5%).

Phase III Trials of S-1 Monotherapy vs S-1 in Combination

Based on the results obtained in the above phase II studies, three large randomized phase III studies, the SPIRITS trial, the TOP-002 trial, and the JACCRO GC03 trial, were conducted independently to compare data with that of S-1 monotherapy. In the SPIRITS trial,[19] chemotherapy-naïve patients with AGC were randomly assigned to receive either S-1 plus cisplatin or S-1 alone. In the patients assigned to receive S-1 plus cisplatin, the S-1 (40–60 mg depending on the patient's body surface area) was given orally, twice daily for 3 consecutive weeks, and 60 mg/m^2 cisplatin was given intravenously on day 8, followed by a 2-week rest period within a 5-week cycle. Patients assigned to receive S-1 alone were given the same dose of S-1 twice daily for 4 consecutive weeks, followed by a 2-week rest period, within a 6-week cycle. The primary endpoint was overall survival and the secondary endpoints were PFS, proportion of responders, and safety. Of the 305 patients enrolled, 7 were ineligible or withdrew consent, 148 patients were assigned to the S-1 plus cisplatin group, and 150 were assigned to the S-1 alone group. Median overall survival was significantly longer in the patients assigned to receive S-1 plus cisplatin than in those assigned to receive S-1 alone (13.0 vs 11.0 months, respectively; hazard ratio, 0.77; 95% confidence interval, 0.61–0.98; $P = 0.04$). The PFS was significantly longer in the patients assigned to receive S-1 plus cisplatin than in those assigned to receive S-1 alone (median PFS, 6.0 months vs 4.0 months, respectively; $P < 0.0001$). Moreover, of the 87 patients with target tumors, assigned to receive S-1 plus cisplatin, 1 showed a CR and 46 showed a PR (total response rate, 54%), and of the 106 patients with target tumors, assigned to receive S-1 alone, 1 showed a CR and 32 showed a PR (total response rate, 31%). Grade 3 or 4 adverse events including leukopenia, neutropenia, anemia, nausea, and anorexia were reported in the group assigned to S-1 plus cisplatin rather than in the group assigned to S-1 alone. There were no treatment-related deaths in either group. Based on this trial, S-1 plus cisplatin became regarded as a new standard first-line treatment for patients with AGC in Japan.

A randomized phase III trial was conducted to evaluate the efficacy and safety of IRIS (S-1/CPT-11) vs S-1 for AGC.[20] Patients with previously untreated AGC were randomized to Arm A (oral S-1, 80 mg/m^2 on days 1–28, every 6 weeks) or Arm B (IRIS: oral S-1,

80 mg/m^2 on days 1–21; and intravenous irinotecan, 80 mg/m^2 on days 1 and 15, every 5 weeks) by dynamic allocation. Treatment was continued unless disease progression or unacceptable toxicity was observed. The primary endpoint was overall survival and the secondary endpoints were 1-year survival, response rate, and toxicity. As a result, 326 patients were randomized to Arm A (162 patients) or Arm B (164 patients), with a final 315 evaluable patients (160 in Arm A and 155 in Arm B). The patients' characteristics were well balanced in the two groups. By the end of the trial, 247 events (78%) had been observed. Although the MST of the Arm A patients was 318 days (95% confidence interval, 286–395) and that of the Arm B patients was 389 days (95% confidence interval, 324–458), Arm B did not show significant superiority to Arm A (log-rank test P = 0.23; hazard ratio = 0.86). The 1-year survival rates were 44.9% in Arm A and 52.0% in Arm B. The response rates were significantly different, being 26.9% in Arm A vs 41.5% in Arm B (chi-square test; P = 0.035) in 187 RECIST (Response Evaluation Criteria In Solid Tumors) evaluable patients. The most common grade 3/4 toxicities in Arm A vs Arm B were neutropenia (10.6% vs 27.1%), diarrhea (5.6% vs 16.1%), anorexia (18.8% vs 17.4%), nausea (5.6% vs 7.1%), and vomiting (1.9% vs 3.2%). Based on this trial, IRIS achieved MST and was better tolerated; however, IRIS did not show significant superiority to S-1 alone in terms of the overall survival. Thus, IRIS could not become a first-line treatment for AGC.

A randomized phase III study comparing S-1 alone with the S-1/docetaxel combination is ongoing through the JACCRO GC03 trial.[21] This study is a prospective, multicenter, multinational (Korea and Japan), nonblinded, randomized, phase III study of patients with AGC. Patients are randomly assigned to receive 3-week cycles of Treatment Arm A (docetaxel and S-1) or 6-week cycles of Treatment Arm B (S-1 only). The primary objective of the study is to compare the median overall survival of the test arm (docetaxel and S-1) with that of the control arm (S-1 only) in patients with AGC. The secondary objectives are to assess the time to tumor progression (TTP), defined as the time from randomization to the date of first documentation of progressive disease (PD); to determine the clinical response (RR = response rate), defined as the sum of the CR and PR according to the RECIST; and to evaluate the safety of the two regimens. It was expected that 628 patients (314 in each treatment arm) would be enrolled in this trial and this has been exceeded, with 628 patients from 103 centers confirmed in September 2008. The first author of this review is a principal participating investigator in this trial, the results of which will be available in 2010.

Future Perspectives of Standard Chemotherapy

If the results of the S-1/docetaxel combination are positive, both S-1/docetaxel and S-1/cisplatin will offer standard care options for AGC. A triplet of the S-1/cisplatin/docetaxel combination is expected as the next candidate of the standard regimen.[22] The replacement of heavy metals from cisplatin to oxaliplatin in the combination with S-1 is also expected. Some molecular target agents have already been investigated for AGC. These agents of the new generation are expected to make revolutionary progress in chemotherapy for unresectable or recurrent GCs.

Second-Line Chemotherapy

Weekly paclitaxel or cisplatin/CPT-11 is widely used as second-line chemotherapy, but there is no established regimen for patients with AGC failing to respond to, or with progression after, first-line chemotherapy. Although there are some phase III studies ongoing, the treatment of S-1 refractory GC remains controversial with regard to whether S-1 should be continued as a second-line. After the successful adjuvant S-1 results (ACTS-GC trial),[23] the same problem will arise in patients receiving adjuvant S-1 for recurrence. The JACCRO GC05 trial is a randomized phase II/III trial of second-line chemotherapy comparing CPT-11 monotherapy with the S-1/CPT-11 combination for S-1 refractory GC. We expect that the results of this study will resolve the controversy.

Neoadjuvant Chemotherapy (NAC)

Japanese surgeons can control N2 lymph node metastasis by standard gastrectomy with D2 dissection. Neoadjuvant chemotherapy for high-risk patients with AGC is important to increase the chance of curative resection and make unresectable GC tumors resectable by downstaging the tumor. Tumors with H0, P0, T3, T4, or N3 are most suitable for this therapy. The downstaging of lymph node metastasis of N3 or over to controllable N2 is the main target of NAC. Other distant metastasis, such as hepatic, lung, or peritoneal dissemination, is usually treated by chemotherapy first, and is not a target of NAC. S-1/cisplatin is widely used for the NAC regimen based on the high response rate reported in a phase II trial.[15] Randomized controlled phase III studies are needed in conjunction with accurate staging of the disease by laparoscopy. The results of histopathologic examination of resected materials following preoperative chemotherapy are thought to be an indicator of chemosensitivity in the postoperative adjuvant setting.

As yet, there is no clear evidence of the utility of NAC for GC, but its benefits will be proved soon by randomized controlled trials.

Adjuvant Chemotherapy

Before 2004, no positive results of adjuvant chemotherapy for curatively resected GC were reported. In the United States, the INT-0116 showed that adjuvant chemoradiation prolonged survival and relapse-free survival.[24] However, most of the patients in this study underwent D0 or D1 surgery, whereas only 10% underwent D2 lymphadenectomy. The European MAGIC trial, performed mainly in the United Kingdom, showed that perioperative and postoperative chemotherapy with ECF significantly prolonged overall survival and progression-free survival. In that study, D2 surgery was not the standard procedure, as it is in Japan. Comparisons of adjuvant chemotherapy vs surgery alone after D2 surgery in Japan were not positive.

In 2007, Nakajima et al.[25] reported positive results of adjuvant UFT based on the NSAS GC trial. In this trial, patients with TNM (tumor node metastasis) stage T2 N1-2 GC were randomly assigned to undergo surgery alone or to undergo surgery followed by postoperative UFT 360 mg/m^2 per day orally for 16 months. However, this trial was terminated before the target number of patients had been reached as accrual was slower than expected, with 190 patients registered and 95 randomized to each group. Nevertheless, after a median follow-up of 6.2 years, the overall and relapse-free survival rates were significantly higher in the surgery+chemotherapy group (hazard ratio for overall survival 0.48, $P = 0.017$; hazard ratio for relapse-free survival 0.44, $P = 0.005$). Furthermore, in 2007 Sakuramoto et al.[23] reported the success of adjuvant S-1 chemotherapy in patients with curatively resected GC. Patients with stage II or III GC who underwent gastrectomy with D2 dissection were randomly assigned to undergo surgery followed by adjuvant therapy with S-1 or to undergo surgery only. In the surgery+S-1 group, S-1 was started within 6 weeks after surgery and continued for 1 year. The treatment regimen consisted of 6-week cycles in which, in principle, 80 mg/m^2 of oral S-1 per day was given for 4 weeks and no chemotherapy was given for the following 2 weeks. There were 529 patients assigned to the surgery+S-1 group and 530 patients assigned to the surgery-only group between October 2001 and December 2004. The trial was stopped on the recommendation of independent data and the safety monitoring committee, because the first interim analysis, performed 1 year after enrollment was completed, showed that the surgery+S-1 group had a higher overall survival rate than the surgery-only group ($P = 0.002$). Analysis of follow-up data showed that the 3-year overall survival rate was 80.1% in the surgery+S-1 group and 70.1% in the surgery-only group. The hazard ratio for death in the surgery+S-1 group vs the surgery-only group was 0.68 (95% confidence interval, 0.52–0.87; $P = 0.003$). Adverse events of grade 3 or grade 4 (defined according to the Common Toxicity Criteria of the National Cancer Institute), which were relatively common in the surgery+S-1 group, were anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%). It was concluded that S-1 is an effective adjuvant treatment for patients who have undergone a D2 dissection for locally advanced GC.

Conclusions

1. The standard regimen now used for AGC in Japan is the S-1/cisplatin combination, and we are awaiting the trial results about S-1/docetaxel combination chemotherapy. If the results of this S-1/docetaxel combination are positive, both S-1/docetaxel and S-1/cisplatin will offer standard care options for AGC.
2. Weekly paclitaxel or cisplatin/CPT-11 is widely used as second-line chemotherapy after refractory S-1, but there is still no standard second-line regimen until ongoing phase III results are reported.
3. Neoadjuvant chemotherapy for high-risk patients with AGC is important to increase the chance of curative resection and make unresectable GC tumors resectable by downstaging the tumor. Downstaging of N3 (or more) lymph node metastasis to controllable N2 is the main target of NAC.
4. The standard chemotherapy for T2 N1-2 GC after D2 dissection is adjuvant UFT, and that for stage II, III GC after D2 dissection is adjuvant S-1.

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