Compared with other Japanese Phase II clinical trials of other fluoropyrimidines or cytotoxic agents, S-1 monotherapy was extremely high (see *Table 2*). In the first Japanese Phase III clinical trial conducted by the Japan Clinical Oncologist Group (JCOG) in patients with unresectable advanced/recurrent gastric cancer (JCOG 9205), 5-FU continuous infusion (800 mg/m$^2$ 24 h continuous infusion (CI), D1–5, q4w) was the standard treatment. The test arms were tegafur/uracil (375 mg/m$^2$ daily) plus mitomycin C (5 mg/m$^2$ weekly) and 5-FU (800 mg/m$^2$, 24 h CI, D1-5) plus cisplatin (20 mg/m$^2$, D1-5, q4w). 5-FU plus cisplatin did not show superiority to 5-FU continuous infusion.[13] Therefore, the control arm with 5-FU continuous infusion (800 mg/m$^2$ 24 h CI, D1–5, q4w) was selected in the next Phase III clinical trial, JCOG 9912. In this study, the test arms were S-1 monotherapy (80, 100 and 120 mg/body/day for body surface area <1.25 m$^2$, 1.25 - < 1.5 m$^2$ and ≥ 1.5, respectively, D1-28, q6w) and irinotecan (70 mg/m$^2$, D1, 15) plus cisplatin (80 mg/m$^2$, D1, q4w) with a primary endpoint of overall survival (OS). S-1 monotherapy was shown to be non-inferior to 5-FU continuous infusion; the median survival time for S-1 was 11.4 months and the hazard ratio (HR) relative to 5-FU continuous infusion was 0.832 (95 % CI: 0.68–1.01, p=0.0005).[14]

Interestingly, in JCOG 9912 study, the expression of DPD in patients with diffuse type gastric cancer receiving S-1 (poorly differentiated carcinoma, signet-ring cell carcinoma, mucinous adenocarcinoma, n=82) was significantly higher than in patients with intestinal type (papillary or tubular adenocarcinoma, n=86) following the Lauren classification (p<0.001). Hence, 5-FU may not be sufficient for this group of patients. The median progression-free survival (PFS) among 5-FU- or S-1-treated patients with tumours expressing higher levels of DPD was 2.1 and 4.2 months, respectively (HR=2.05; 95 % CI: 1.13–3.71; p=0.016) and S-1 maintained its efficacy in patients with both high and low DPD expression.[15]

The S-1 Plus cisplatin versus S-1 In RCT In the Treatment for Stomach cancer (SPIRITS) study investigated the efficacy of S-1 (80–120 mg/day, D1–21) plus cisplatin (60 mg/m$^2$, D8, q5w) compared with S-1 monotherapy (80–120 mg/day, D1–28, q6w).[16] This was the first trial to demonstrate the direct survival benefit of S-1 plus cisplatin compared with S-1 monotherapy. S-1 plus cisplatin showed statistically significant survival benefits. The survival rates were 54 % for S-1 in combination with cisplatin versus 47 % for S-1 monotherapy at one year and 24 % for the combination regimen versus 15 % for monotherapy at two years (p=0.04, HR=0.77, 95 % CI; 0.61–0.98).

On the basis of results from these two pivotal trials, S-1 monotherapy appears to be non-inferior to 5-FU. The S-1 plus cisplatin combination however, is superior to S-1 monotherapy. The S-1 plus cisplatin combination regimen has therefore been considered as a standard chemotherapy for unresectable (advanced or metastatic) gastric cancer patients. In the Japanese gastric cancer treatment guidelines 2010,[17] S-1 plus cisplatin is recommended for gastric cancer as a first-line treatment. When S-1 plus cisplatin is considered inappropriate, either S-1 or 5-FU should be delivered as a single agent, depending on the condition of the patients.

In a Phase III trial of gastric cancer, S-1 was compared with S-1 plus irinotecan. Irinotecan was administered at a dose of 80 mg/m$^2$ on day 1 and day 15, every five weeks.[18] The primary endpoint was also OS. The HR was 0.856 (p=0.233), the median OS were 10.5 months for S-1 alone and 12.8 months for S-1 with irinotecan and the one-year survival rates were 44.9 and 52.0 %, respectively; however, these were not significantly different. In a further trial, S-1 alone was compared with S-1 plus docetaxel in which the primary endpoint was OS. Docetaxel (40 mg/m$^2$, D1) plus S-1 (80–120 mg/day, D1–14, q4w) were administrated in the patients. The HR was 0.88. As presented during the last ESMO meeting, the follow up of this trial showed a statistically significant improvement of the overall survival in favour of the S-1 + docetaxel regimen (12.5 versus 10.8 months, p=0.0319).[27b] In recent Phase III trials, S-1 monotherapy showed very similar outcomes with median PFS of four months and median OS of 11 months.[16,18,27]

**Table 2: The Response Rate of Japanese Phase II Studies in Advanced Gastric Cancer**

| Agent | Number of Patients | Response Rate (%) |
|---|---|---|
| Doxifluridine (Niitani et al., 1985)[19] | 140 | 14.3 |
| Tegafur/uracil (Ota et al., 1988)[20] | 188 | 27.7 |
| S-1 (Sakata et al., 1998)[11] | 51 | 49.0 |
| S-1 (Koizumi et al., 2000)[12] | 43 | 44.2 |
| Epirubicin (Sakata and Yoshida, 1986)[21] | 31 | 16.1 |
| Cisplatin (Ishibiki et al., 1989)[22] | 68 | 19.1 |
| Irinotecan (Futatsuki et al., 1994)[23] | 60 | 23.3 |
| Docetaxel (Taguchi et al., 1998[24] and Mai et al., 1999[25]) | 66<br>63 | 23.7<br>23.7 |
| Paclitaxel (Yamada et al., 2001)[26] | 60 | 23.3 |

*Source: Data presented by Y Yamada.*

In Japan, S-1 plus cisplatin is currently the standard first-line treatment and 70 to 80 % of patients will eventually receive second-line treatment with irinotecan, docetaxel or paclitaxel monotherapy. More than 50 % of these patients will receive chemotherapy that includes paclitaxel.

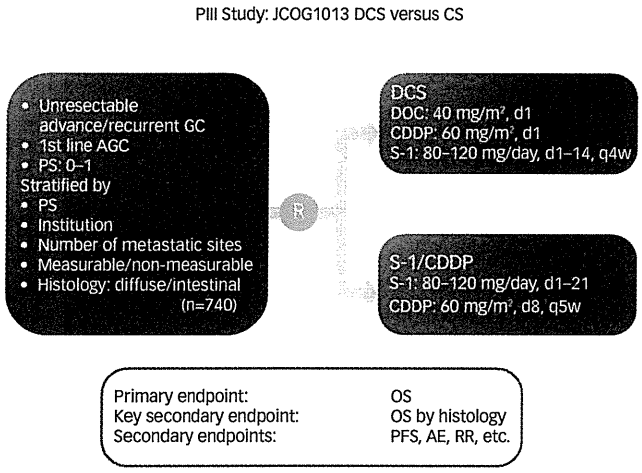
Another promising gastric cancer treatment regimen is S-1 plus oxaliplatin (SOX). In a Phase II study investigating this combination, Oxaliplatin (100 mg/m$^2$, D1) plus S-1 (80–120 mg/m$^2$, D1–14, q3w) were administrated in the patients.[28] The response rate was 59 %. The most commonly observed grade 3 or 4 toxicities were neutropenia in 22 % and thrombocytopenia in 13 % of patients. The median OS was 16.5 months. This trial led to an ongoing Phase III trial (n=680) in Japan that is to evaluate non-inferiority of PFS and OS comparing SOX versus S-1 plus cisplatin.

An alternative approach to gastric cancer treatment was evaluated in a Phase I/II trial in which patients received a triplet of docetaxel, cisplatin and S-1 (DCS). Docetaxel (40 mg/m$^2$) and cisplatin (60 mg/m$^2$) were given on day 1 of 28-day cycle; S-1 (40 mg/m$^2$) was given twice daily on days 1–14.[29] The most commonly observed grade 3/4 toxicity was neutropenia in 70 % of patients. The median PFS was 8.7 months and the median OS was 18.5 months. This DCS regimen showed marked efficacy against intestinal and diffuse types of gastric cancer. In this study, down-staging of gastric cancer was achieved in nine (19 %) of 48 patients who responded to DCS.

The DCS is also being compared with a S-1 and cisplatin and combination in another ongoing Phase III trial in patients with unresectable, recurrent or advanced gastric cancer in Japan (JCOG 1013) (see *Figure 2*). The aim of this study is to evaluate superiority of OS (n=740).

For HER2-positive gastric cancer patients, there are currently three Phase II clinical trials with S-1 in progress in Japan and Southeast Asia

**Figure 2: Schema of Phase III Trial Comparing the DCS with Cisplatin and S-1 Combination in Patients with Unresectable, Recurrent or Advanced Gastric Cancer in Japan**




*AE = adverse event; AGC = advanced gastric cancer; CDDP = cisplatin; CS = cisplatin and S-1; DCS = docetaxel, cisplatin and S-1; DOC = docetaxel; GC = gastric cancer; JCOG = Japan Clinical Oncology Group; OS = overall survival; PFS = progression-free survival; PS = performance status; RR = response rate.*

(n=25–60). In two of them, a combination of S-1 plus cisplatin plus trastuzumab is being evaluated and in the other S-1 plus trastuzumab is being investigated in elderly patients.

While S-1 plus cisplatin is the current standard regimen for gastric cancer in Japan, SOX and DCS regimens are likely to become more widely used in gastric cancer once Phase III clinical trial results become available in the near future. Phase III data supporting the use of these promising combinations in gastric cancer are now awaited with interest. In clinical use, combination regimens that include S-1 are likely to extend the lives of many patients with advanced gastric cancer.

## Established Benefits of S-1 Confirmed in Western Populations

Asian patients, particularly the Japanese, have a markedly different metabolism of anti-cancer drugs compared with Western populations. This phenomenon has been observed with drugs such as 5-FU for which the doses used in Asian patients are much higher than are normally used in Caucasians.

The combination of S-1 and cisplatin is highly active in Japanese patients with advanced gastric cancer. Following the discovery of regional dose variations of one of the S-1 components, it was necessary early in drug development to define the optimal dosing of both S-1 and cisplatin in combination for use in a Caucasian patient population. This necessitated a Phase I pharmacokinetic study in which a combination of S-1 and cisplatin were used to treat advanced gastric carcinoma.[30] In the Japanese population, given an S-1 dose of 32 to 40 mg/m$^2$, the exposure, as expressed as the AUC, is around 700 ng x h/mL.

In the Caucasian population, to reach a similar AUC with an acceptable tolerability, it is necessary to decrease to a dose of 25 mg/m$^2$ in combination with cisplatin and it is necessary to decrease to 30 mg/m$^2$ in monotherapy.[30b]

The design of this Phase I trial allowed various levels of dose escalation, and concluded that the recommended doses were 25 mg/m$^2$ for S-1 and 75 mg/m$^2$ for cisplatin. At these doses, the incidence of grade 3/4 toxicities was very low although this was a small Phase I study; 6 patients receiving 25/75 mg/m$^2$/dose S-1/cisplatin, six receiving 30/60 mg/m$^2$/dose and three receiving 30/75 mg/m$^2$. At the highest doses the incidence of grade 3/4 toxicities was greater. These findings led to the initiation of a single-arm Phase II study that investigated the efficacy of the recommended dose based on the Phase I trial: 25 mg/m$^2$ of S-1 twice daily (BID) for three weeks and cisplatin on day 1 at 75 mg/m$^2$.[31,32] This treatment improved the time to disease progression to one year; one-year survival rate was 42 % and the two-year survival rate was 21 %. The efficacy data, as reviewed by an independent committee, showed that there was a response rate of 55 % and this was confirmed by time to progression and duration of response. The results of 25 mg/m$^2$ of S-1 BID plus cisplatin 75 mg/m$^2$ combination confirmed the efficacy of this treatment.

The S-1/cisplatin combination showed an advantageous tolerability profile in which grade 3/4 neutropenia in 19 % of the patients was the main finding. The remaining toxicities were non-haematologic types. These consisted of fatigue/asthenia (grade 3/4) in 24 %, diarrhoea (grade 3 /4) in 13 %, a low incidence of stomatitis, and a low incidence of febrile neutropenia. This is considered to be an acceptable toxicity profile.

The findings of this study led to the FLAGS study, a multi-centre, international Phase III trial focussing on a Caucasian population with advanced metastatic gastric cancer.[3] This study used the recommended doses that were identified in the Phase I study and confirmed in the Phase II: S-1 at 25 mg/m$^2$ orally BID for three weeks, with one week of rest plus cisplatin at 75 mg/m$^2$. This was compared with the conventional 5-FU/cisplatin regimen in which 5-FU was given at 1,000 mg/m$^2$/day over five days and cisplatin was given at a dose of 100 mg/m$^2$ on day 1 every four weeks. A total of 1,053 patients were randomised and the patient population was stratified according to the extent of disease, prior adjuvant chemotherapy and measurable versus non-measurable disease; the primary endpoint was overall survival. The statistical analysis plan aimed to demonstrate improvement in median survival from 8.5 months in the cisplatin/5-FU arm to 10.5 months in the experimental arm of cisplatin S-1, corresponding to a HR of 0.81. There was also a delayed endpoint of non-inferiority on OS for which the upper limit was 1.10 to reach statistical significance and to retain potentially 74 % of the effect of cisplatin/5-FU. In parallel, the secondary endpoints of the FLAGS study were PFS, safety, time to treatment failure (TTF), response rate, duration of response, time to tumour response, time to tumour progression, clinical benefit and the quality of life using the FACT gastric scale. The patient population was well balanced in both arms. The majority of patients were male and importantly, 86 % were Caucasian.

The cancers were primarily of the stomach, a few subjects had gastro-oesophageal junction disease, and the diffuse histological type was slightly more frequently than the non-diffuse type. Metastatic disease was present in almost all the patients with two-thirds of the patients having more than two metastatic sites and most were measurable. Very few patients had received prior adjuvant chemotherapy and approximately one-third had prior stomach resection.

There was no major difference in treatment compliance between the two arms and the median number of cycles per patient was four, ranging from one to 28 or one to 24. The dose intensities of S-1 and

5-FU were similar (92 and 95 %, respectively). The duration of treatment was also similar to the planned regimen in both arms.

Toxic death under treatment was three times higher in the cisplatin/5-FU arm as compared with S-1/cisplatin. For OS, the first primary objective of superiority was not met (HR= 0.92, *Figure 3*). However, the calculated level of OS non-inferiority was met and showed that S-1/cisplatin is non-inferior to 5-FU/cisplatin (p=0.0068). For the secondary endpoints, PFS was not superior (HR=0.99) but TTF was (HR=0.87, p=0.032) (see *Figure 3*). The Forest plot in Figure 4 shows that no patient subgroups clearly benefited from either treatment regimen. There are slight advantages for both S-1 and 5-FU but no overall trend towards either treatment for any subgroup. There were similar overall response rates for S-1/cisplatin and 5-FU/cisplatin of 29.1 and 31.9 %, respectively. The duration of response was slightly longer for S-1/cisplatin compared with 5-FU/cisplatin.

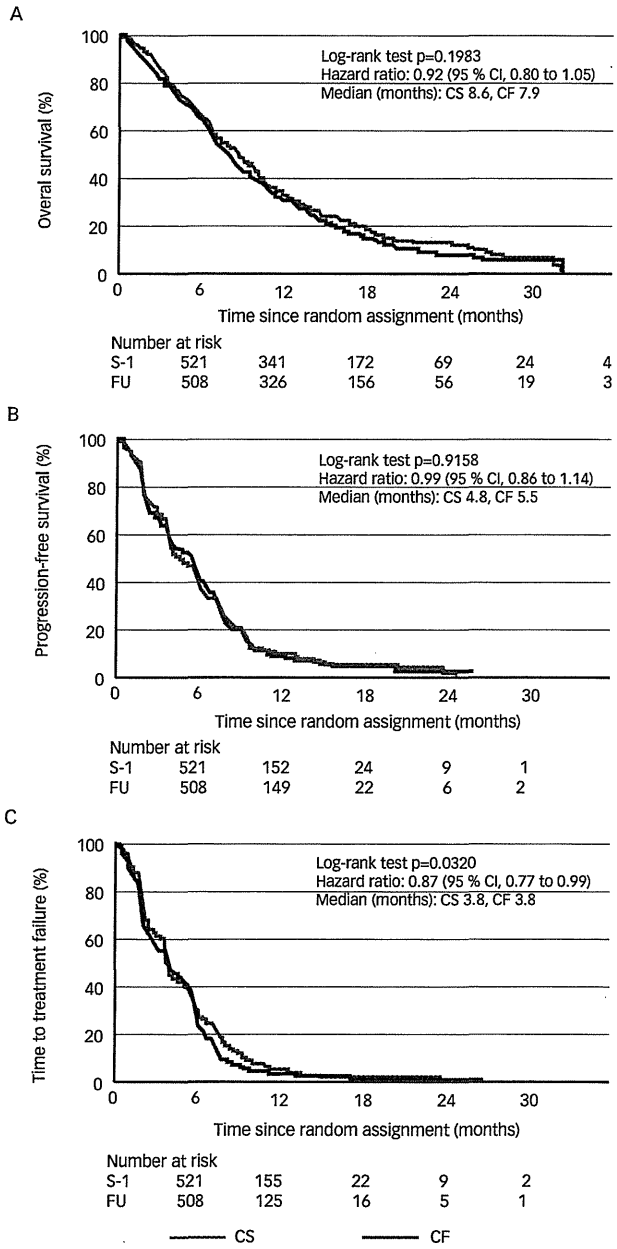
The incidence of severe neutropenia was significantly different between the two treatment groups: approximately 35 % for S-1/cisplatin compared with almost 70 % for 5-FU/cisplatin. There was also a clear advantage in terms of myelosuppression, reflected in a significant reduction of thrombocytopenia and a lower incidence of febrile neutropenia in patients receiving S-1/cisplatin. These results therefore clearly confirm the low myelotoxicity profile of S-1 that was observed in the initial Phase I trial.

In terms of non-haematological toxicity, there was a significant difference in the incidences of diarrhoea (all grades) and the use of anti-diarrhoeal medication was significantly reduced in the cisplatin/S-1 arm compared with the 5-FU/cisplatin arm. There was also a reduction in the incidence of dehydration which is quite often associated with diarrhoea and interestingly, a very low incidence of stomatitis, mucosal inflammation (mostly conjunctivitis), hypophosphatemia and hypomagnesemia with S-1/cisplatin compared with the 5-FU/cisplatin. Therefore the tolerance profile of cisplatin/S-1 appears to be significantly better than that of 5-FU/cisplatin.

In the FLAGS study, renal toxicity appeared to be reduced in the S-1/cisplatin arm compared with 5-FU/cisplatin. The lower dose of cisplatin used in the S-1 arm (75 mg/m$^2$) versus the IV 5-FU arm (100 mg/m$^2$) seems to be the main driver of this advantage. Liver function tests showed slight increases in bilirubin as well as all grades of liver-related adverse events for S-1/cisplatin compared with cisplatin/5-FU. Liver impairment showed no statistical difference between treatments and most of this was not associated with symptoms. Thus there was a significantly reduced incidence of serious adverse events with S-1/cisplatin compared with 5-FU/cisplatin. Death related to treatment was significantly reduced by half with S-1/cisplatin. S-1/cisplatin therefore clearly has a superior tolerability profile than 5-FU/cisplatin but with similar efficacy.

It has been observed in previous studies and in general clinical experience that patients prefer oral fluoropyrimidine to the IV form, mostly as a result of improved quality of life. In the FLAGS study, three quality of life parameters were significantly improved in the S-1/cisplatin group.[3] These included the time to more than 5 % weight loss and the physical well being subscale within the FACT Gastric Scale. In addition, the use of anti-diarrhoeal medication was significantly reduced by 40 % with S-1/cisplatin and the use of colony stimulating factors which are associated with neutropenia was

**Figure 3: Kaplan-Meier Plot of Overall Survival by the Two Treatment Arms in the FLAGS Study**

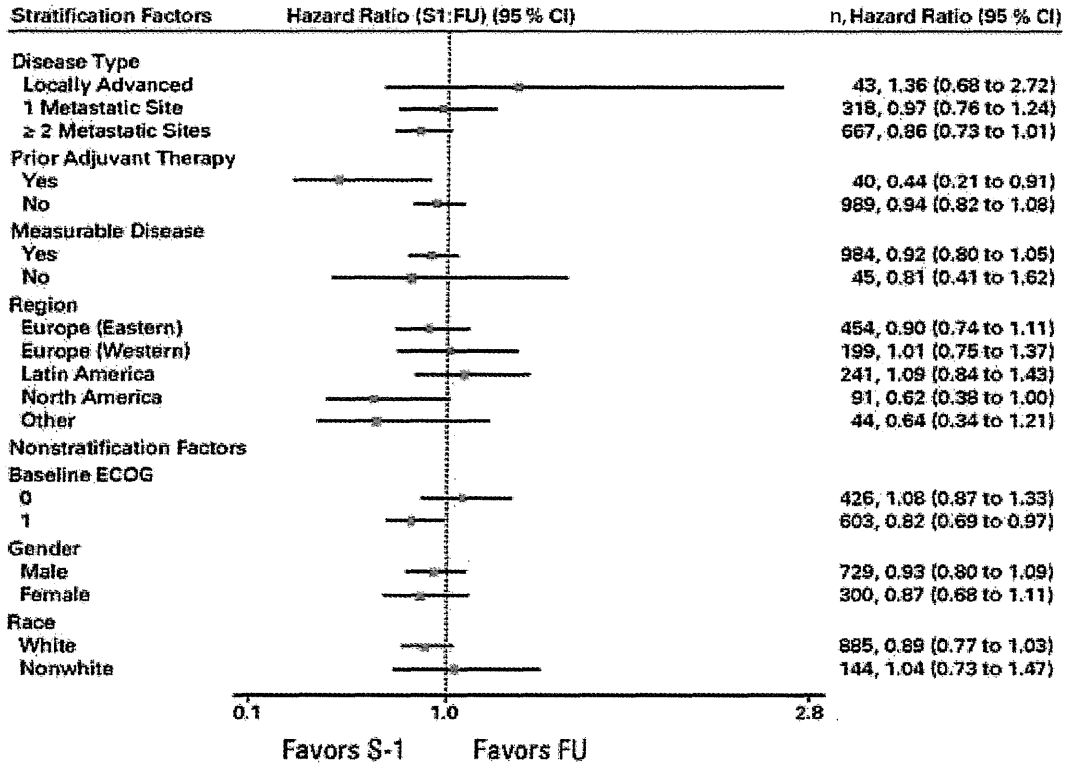



*A: Overall survival; B: progression-free survival; C: time without treatment failure. CF = cisplatin/5-FU; CS =cisplatin/S-1; FU = 5-fluorouracil; S-1 = tegafur/gimeracil/oteracil combination (Teysuno®). Source: Ajani et al., 2010.*[3]

reduced by 49 %. S-1/cisplatin therefore clearly provides advantages in terms of quality of life, the need for supportive care, anti-diarrhoeal drugs and colony stimulating factor.[33,33b]

The number of hospitalisations also differed between the treatment groups in the FLAGS study. Patients receiving oral drug treatments spent fewer days in hospital and needed to attend only to receive cisplatin. This is reflected in the number of patients that needed to be hospitalised to receive the S-1/cisplatin combination (67.4 %) compared with those receiving 5-FU/cisplatin (80.7 %). Overall, the median number of days patients were hospitalised was twice as high in the 5-FU/cisplatin group (24 days) compared with S-1/cisplatin, (11 days).

**Figure 4: Forest Plot of Pre-planned Stratification Factors for Overall Survival in the FLAGS Study**




*ECOG = Eastern Cooperative Oncology Group; FU = 5-fluorouracil; S-1 = tegafur/gimeracil/oteracil combination (Teysuno®). Source: Ajani et al 2010.[3]*

In summary, in the FLAGS study, the primary endpoint of superiority in OS was not met, but the comparison of the non-inferiority calculated level of the upper HR limit 1.10 is highly statistically significant when compared with the upper HR limit obtained in FLAGS for OS 1.05 (p=0.0068).[33]

This approach was considered by the Committee for Medicinal Products for Human Use (CHMP) of the European Medical Agency (EMA), who concluded that the benefits of S-1 are greater than its risk and recommended that it be given marketing authorisation in March 2011. Approval was therefore granted for S-1 for the treatment of advanced unresectable metastatic gastric cancer in combination with cisplatin.

## Committed to Filling Knowledge Gaps – The S-1 Development Programme

The FLAGS study provided evidence to support the view that S-1 should be incorporated into treatment strategies for gastrointestinal cancers in Europe. Following an EMA Market Authorisation, S-1 is currently registered as Teysuno® and is already available in Northern European countries including, Denmark, Finland, Norway, Sweden and the UK. It became available in Austria and Germany on the July 1 2012 and other European countries will follow soon.

The projected next step in S-1 development in the US will be the Diffuse Gastric and Esophagogastric Junction Cancer S-1 Trial (DIGEST, NCT 01285557), which uses a similar strategy as the FLAGS study but will look into the superiority of OS for S-1/cisplatin in patients with diffuse type histology. Approximately 60 % of patients in the FLAGS study had the diffuse type of cancers and OS in this group was reported to be better than in those with non-diffuse histology, especially in individuals with lower weight loss. The OS in patients with this histology was 9.0 months for S-1/cisplatin compared with 7.1 months for FU/cisplatin.[34] The trial is being conducted in numerous treatment centres across 20 countries worldwide and plans to recruit at total of 500 patients between 2010 and 2013 with a one-year follow-up.

S-1 may also be used as part of a triplet treatment regimen for gastric cancer but at present there are no data available for Caucasian populations. It remains controversial whether a triplet regimen is needed. However, a meta-analysis demonstrated significant benefit from adding an anthracycline to a platinum and fluoropyrimidine doublet, and ECF (epirubicin plus cisplatin plus protracted infusion 5-FU) is among the most active and well-tolerated regimens.

Docetaxel increases the activity of 5-FU/cisplatin, but is also more toxic when used in a three-weekly regimen, with 29 % complicated neutropenia reported.[35] A randomised Phase II study demonstrated maintained activity with reduced toxicity when a weekly docetaxel schedule was employed in combination with cisplatin and infused 5-FU or capecitabine.[36]

The substitution of capecitabine (X) for 5-fluorouracil (F) and oxaliplatin (O) for cisplatin (C), in the ECF regimen was examined in the recent UK National Cancer Research Institute (NCRI) Randomised ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) trial, which demonstrated non-inferiority between ECF, ECX, EOF and EOX. The EOX regimen was associated with a longer OS (11.2 versus 9.9 months, HR 0.80, 95 % CI 0.66–0.97; p=0.02) than the reference ECF regimen and the rate of thromboembolism was also significantly reduced by the oxaliplatin substitution (7.6 % compared with 15.1 %, p=0.0003).[37]

These data prompted a Phase I study to evaluate an epirubicin/oxaliplatin/S-1 (EOS) combination. To date, this has recruited eight patients and aims to determine the maximum tolerated dose of S-1, either 20 mg/m$^2$ (dose level 1) or 25 mg/m$^2$ (dose level 2) combined with epirubicin at 50 mg/m$^2$ and oxaliplatin at 130 mg/m$^2$. This trial will allow a recommended dose of S-1 in an EOS regimen to be established and it will be possible therefore to analyse this EOS regimen in a later Phase III trial and compare it directly with EOX.

A recent study combined S-1 with oxaliplatin in a Caucasian population with advanced solid tumours.[38] In this study, patients received one of two treatment schedules. Schedule A consisted of S-1 25 mg/m$^2$ BID for 14 consecutive days then a seven-day recovery period in a 21-day cycle and bevacizumab 7.5 mg/kg IV on day 1 of each three-week cycle and oxaliplatin 130 mg/m$^2$ IV on day 1 of each three-week cycle. Schedule B consisted of S-1 35 mg/m$^2$ BID on day 1 for seven consecutive days then a seven-day recovery period in a 14-day cycle and bevacizumab 5 mg/kg IV on day 1 of each two-week cycle and oxaliplatin 85 mg/m$^2$ IV on day 1 of each two-week cycle. The toxicity data show that higher dosages of oxaliplatin also increase grade 1 and 2 peripheral sensory neuropathy. From this trial, therefore, it can be concluded that S-1 and oxaliplatin can be administered with the biological bevacizumab and perhaps other biologics, with acceptable safety and tolerability without evidence of pharmacokinetic interactions.

In another randomised trial conducted in Asia, SOX was compared with CAPOX in the treatment of gastric cancer.[6] Both the SOX and CAPOX regimens were equally active and well tolerated in advanced gastric cancer patients. Grades 3/4 neuropathy, nausea, vomiting and asthenia were less frequent with SOX and as anticipated, HFS at any grade was more frequent for CAPOX (SOX = 3 %; CAPOX = 25 %, p=0.001). Therefore two viable treatments may reduce the risk of HFS. One is the cisplatin/S-1 regimen in a four-weekly regimen and the other is the SOX regimen which is the 130 mg/m$^2$ oxaliplatin with 25 mg/m$^2$ S-1 BID regimen in a three-weekly cycle.

Finally, S-1 is also being developed for use in colorectal cancer and ongoing studies in Asia are comparing SOX with other combinations such as folinic acid/fluorouracil/oxaliplatin (FOLFOX).

## Conclusion

The 13 years of clinical experience of S-1 in advanced gastric cancer in Japan has shown that the use of this new oral formulation of FU in combination therapy consistently improves survival whilst reducing toxicities and improving tolerability. Non-haematological and haematological adverse events such as diarrhoea and neutropenia are substantially reduced with S-1 compared with other treatments. Pharmacokinetic studies in Western populations showed a marked contrast in the metabolism of S-1 between Japanese and Caucasian populations necessitating substantial dose reductions in Europe to achieve the same AUC values as seen in Japan. This emphasises the importance of independent development programmes for chemotherapy in both Asian and Caucasian patients.

The FLAGS study demonstrated non-inferiority of the S-1 combination versus the 5-FU combination for OS. However, the most important finding from this study was the superior safety profile of the S-1 treatment, making S-1 a suitable replacement for 5-FU in gastric cancer treatment. The results of the DIGEST and other studies are awaited with interest and will help define whether S-1 is suitable for the treatment of more diffuse type tumours and whether it is appropriate as part of a triplet regimen. S-1 has also been investigated in the treatment of solid tumours and in combination with oxaliplatin in which it also shows advantageous safety performance compared with capecitabine regimens. It is therefore likely that fluoropyrimidine-containing combinations, and especially S-1-containing treatments, will continue to be used in gastric cancer treatment for the foreseeable future. ■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ORIGINAL ARTICLE

# Leptomeningeal carcinomatosis associated with gastric cancer

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**Abstract**
*Background* Leptomeningeal carcinomatosis (LMC) is a rare but devastating complication of gastric cancer.
*Methods* The subjects were 12 gastric cancer patients who were diagnosed as having LMC at the Shizuoka Cancer Center between October 2002 and March 2009. We conducted a retrospective survey of the medical records of the study subjects and collected data on the clinical features, treatment modalities employed/outcomes, and survival of the patients.
*Results* Of the 12 patients, 9 (75%) were male, and the median age was 63 years. Histopathologically, the majority of the patients (83%) had diffuse-type adenocarcinoma. At the time of diagnosis of the LMC, the other major sites of metastasis were the peritoneum (75%) and lymph nodes (50%). The median duration from the diagnosis of gastric cancer to the diagnosis of LMC was 15.6 months. While the treatment strategy changed with time, intrathecal chemotherapy ($n = 10$), followed by whole brain irradiation ($n = 7$) and subsequent ventriculo-peritoneal shunt ($n = 3$) was performed in 10 of the patients. Improvement of neurological functions was observed in 6 of the 10 patients. The median overall survival time from the diagnosis of LMC in all the 12 patients was 60 days. One patient survived for a considerably long period of 532 days.
*Conclusions* Multidisciplinary treatment, including ventriculo-peritoneal shunt for LMC secondary to gastric cancer, may benefit selected patients, but further accumulation of clinical cases is necessary.

**Keywords** Gastric cancer · Leptomeningeal carcinomatosis · Intrathecal methotrexate therapy · Whole brain irradiation · Ventriculo-peritoneal shunt

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## Introduction

Leptomeningeal carcinomatosis (LMC) complicating solid tumors is most often seen in patients with breast and lung cancer and melanoma, and it is a rare complication in patients with gastric cancer. While LMC is reportedly diagnosed clinically in 2–4% of all cancer patients [1], the prevalence of LMC in gastric cancer patients is as low as 0.14–0.24% [2–4]. However, irrespective of the primary site of cancer, LMC is a devastating complication. There have only been a few reports of LMC complicating gastric cancer.

No standard therapy for LMC has yet been established. The poor general condition of patients with LMC, especially in the presence of consciousness disturbance associated with hydrocephalus, convulsions, etc., makes satisfactory treatment of LMC very difficult. On the other hand, the prognosis of the condition is extremely poor

without treatment. Recently, the efficacy of multidisciplinary treatment for LMC associated with breast and lung cancer, such as intrathecal chemotherapy (ITC) with methotrexate, cytarabine or liposomal cytarabine [5–7], whole-brain irradiation (WBI) [8] and ventriculo-peritoneal shunt (VP shunt) [9], has been reported. However, there are currently no published reports of case series of LMC complicating gastric cancer.

At the Shizuoka Cancer Center, the treatment for gastric LMC has changed with time. ITC alone was administered initially, followed subsequently by the addition initially of WBI, and then more recently of VP shunt performed by neurosurgeons, when indicated, to control the cerebrospinal fluid pressure.

We have encountered some cases of LMC complicating the clinical course in patients with gastric cancer. In the present retrospective study, we report on the clinical features of gastric LMC and also on the outcomes of treatment for LMC secondary to gastric cancer.

## Subjects and methods

The subjects were 12 gastric cancer patients who were diagnosed as having LMC at the Shizuoka Cancer Center between October 2002 and March 2009, and were selected for this study on the basis of the following inclusion criteria: (1) histologically confirmed gastric cancer; (2) LMC confirmed by cerebrospinal fluid (CSF) cytology and/or by magnetic resonance imaging (MRI); (3) no history of other/concurrent malignancies. Patients with LMC caused by direct meningeal invasion from the skull base were excluded. We conducted a retrospective survey of the medical records of the subjects to collect data on the clinical features, treatment modalities employed/outcomes, and survival of the patients.

We administered intraventricular injections of methotrexate at 2 mg/body with prednisolone at 10 mg for 5 consecutive days in all the patients who met the following criteria: (1) age $\leq$75 years; (2) no bleeding tendency; (3) no rapid progression of the lesions other than LMC. Initially, for the first three patients, we undertook no additional therapy after the intraventricular injection of methotrexate. Subsequently, for the next 7 patients who had no previous history of WBI, we added WBI at a total dose of 30 Gy, administered in 10 fractions. For the last three patients, we also performed VP shunt after completion of the WBI. The indication for VP shunt was determined based on the following criteria: (1) improvement of clinical symptoms such as headache, vomiting, and consciousness disturbance after drainage of CSF by a subcutaneous reservoir or lumbar puncture; (2) Radiation Therapy Oncology Group Neurologic Functional Classification (RTOG-NFC) of $\leq$3 (Table 1) [10]; (3) low or moderate cell counts and protein level in the CSF, associated with a reduced risk of shunt obstruction.

**Table 1** Radiation Therapy Oncology Group neurologic function classification

| RTOG neurologic function classification | Description |
|---|---|
| 1 | Able to work or perform normal activities; neurologic findings minor or absent |
| 2 | Able to carry out normal activity with minimal difficulties; neurologic impairment does not require nursing care or hospitalization |
| 3 | Seriously limited in performing normal activities; requiring nursing care or hospitalization; patients confined to bed or wheelchair or have significant intellectual impairment |
| 4 | Unable to perform even minimal normal activities; requiring hospitalization and constant nursing care feeding; Patients unable to communicate or in coma |

## Statistical analysis

The clinical course from the diagnosis of gastric cancer was counted from the date of the initial endoscopy confirming gastric cancer or, in the two cases for whom the date of the initial endoscopy was not available, the date of surgical resection. Overall survival was calculated from the date of diagnosis of the LMC by CSF cytology or MRI to the date of death. The median overall survival was calculated by the Kaplan–Meier method, using StatView software, version 5.0.0 (SAS Institute, Cary, NC, USA).

## Results

### Patients' characteristics

Between October 2002 and March 2009, 14 gastric cancer patients were diagnosed as having LMC. Two of these patients with direct meningeal invasion from a skull base metastasis were excluded. The remaining 12 patients were enrolled as the subjects of this retrospective study.

The characteristics of the subjects are shown in Table 2. Of the 12 patients, 9 (75%) were male, and the median age was 63 years old (range 30–73 years). All patients had neurological symptoms caused by the LMC, and nine patients (75%) had a poor RTOG-NFC of 3 or 4 (Table 1) [10]. All but one patient had diffuse type adenocarcinoma or small cell carcinoma. At the time of diagnosis of the

LMC, other metastatic disease was also observed in 9 patients, including peritoneal dissemination ($n = 8$), lymph node metastasis ($n = 6$), brain metastasis ($n = 2$), bone metastasis ($n = 2$), and liver metastasis ($n = 1$); the remaining three patients showed no evidence of metastasis other than LMC.

Of the 12 patients, 9 had received chemotherapy for gastric cancer prior to the diagnosis of the LMC. At the onset of LMC, the efficacy of the previous chemotherapy was rated as partial response or stable in 7 (78%) patients, progressive disease in one patient, and unevaluated in one patient. Of the remaining 3 patients who had no history of previous chemotherapy, one developed LMC immediately after the gastric cancer diagnosis, and in the other two patients LMC was detected simultaneously with other recurrence(s) after curative surgery. The median duration from the diagnosis of gastric cancer to the diagnosis of LMC was 15.6 months (range 1.0–91.1 months).

**Table 2** Patients' characteristics

| Characteristics | |
|---|---|
| Categories | Number of patients |
| Sex | |
| Male/female | 9/3 |
| Age, years, median (range) | 63 (30–73) |
| RTOG-NFC | |
| 2/3/4 | 2/7/3 |
| Primary tumor | |
| Yes/no | 5/7 |
| Histological type | |
| Intestinal/diffuse/small cell | 1/10/1 |
| Metastatis sites | |
| Peritoneum/lymph nodes/brain/bone/liver/lung | 8/6/2/2/1/1 |
| Number of metastatic sites (except for LMC) | |
| 0/1/2/3/4 | 3/2/2/4/1 |
| Prior chemotherapy | |
| Yes/no | 9/3 |
| Number of prior chemotherapy regimen | |
| 1/2/3/4 | 2/2/4/1 |
| Response to prior chemotherapy at LMC diagnosis | |
| Response or stable/progression/not evaluated | 7/1/1 |

## Clinical symptoms and LMC diagnosis

The most frequent symptom of LMC was headache, and various clinical neurological signs were noted, including consciousness disturbance, cataplexy, vomiting, convulsion, and cerebellar ataxia.

The initial LMC diagnosis was made by gadolinium-enhanced MRI in 8 patients and by CSF cytology in the remaining 4 patients. Finally, leptomeningeal enhancement (Fig. 1) was detected in 10 patients, and the CSF cytology was class IV or V in 9 of the 10 patients in whom the examination was performed.

## Treatment

Among the 12 patients, best supportive care alone was selected for treatment in 2 patients, including one with a past history of WBI for brain metastasis and another who was comatose and developed disseminated intravascular coagulation immediately after being diagnosed with LMC.

The therapeutic modalities applied for the remaining 10 patients were as follows: ITC alone in 3 patients, ITC plus WBI in 4 patients, and ITC plus WBI plus VP shunt in 3 patients. For the intrathecal administration of methotrexate, which was undertaken in all the 10 patients, a subcutaneous (Ommaya) reservoir was implanted in 8 of the patients.

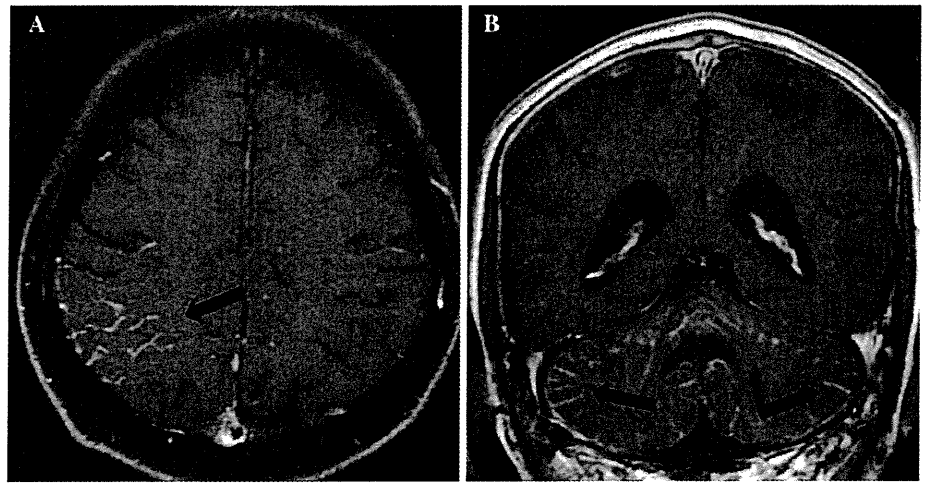


**Fig. 1** Magnetic resonance imaging (MRI) scan finding in LMC. MRI scan of the brain shows peripheral contrast enhancement of the cerebellar (*arrows* in **a**) and cerebral (*arrows* in b) sulci

**Table 3** Toxicity profiles ($n = 10$)

| Toxicity | Grade (NCI-CTC, version 3.0; %) | | | | | |
|---|---|---|---|---|---|---|
| | Intrathecal chemotherapy alone ($n = 3$) | | | Intrathecal chemotherapy + WBI ($n = 7$) | | |
| | 3 | 4 | % grade 3 or lower | 3 | 4 | % grade 3 or lower |
| Luekopenia | 1 | 0 | 33 | 1 | 1 | 29 |
| Neutropenia | 0 | 1 | 33 | 0 | 1 | 14 |
| Hemoglobin | 1 | 0 | 33 | 3 | 0 | 43 |
| Thrombocytopenia | 2 | 0 | 67 | 0 | 1 | 14 |
| AST | 0 | 0 | 10 | 1 | 0 | 14 |
| ALT | 1 | 0 | 33 | 2 | 0 | 29 |
| Febrile neutropenia | 0 | 0 | 0 | 0 | 1 | 14 |
| Headache | 0 | 0 | 0 | 1[a] | 0 | 14 |
| Nausea | 0 | 0 | 0 | 1[a] | 0 | 14 |
| Appetite loss | 0 | 0 | 0 | 1[a] | 0 | 14 |

Five patients (50%) died within 30 days of the last administration of intrathecal methotrexate

*NCI-CTC* National Cancer Institute common toxicity criteria

[a] All the grade 3 or lower headache, nausea, and appetite loss were observed at the beginning of the treatment

**Table 4** Leptomeningeal carcinomatosis with gastric cancer: treatment and outcome

| Case | Age (years) | Sex | RTOG-NFC at diagnosis of LMC | Treatment of LMC | RTOG-NFC after treatment[a] | Transition to home care | Survival after LMC diagnosis (days) |
|---|---|---|---|---|---|---|---|
| 1 | 73 | M | 3 | IT MTX | 4 | No | 14 |
| 2 | 63 | M | 3 | IT MTX | 2 | Yes | 92 |
| 3 | 41 | F | 3 | IT MTX | 2 | Yes | 60 |
| 4 | 70 | M | 3 | IT MTX,WBI | 4 | No | 13 |
| 5 | 30 | F | 3 | IT MTX,WBI | 2 | Yes | 89 |
| 6 | 63 | M | 3 | IT MTX,WBI | 3 | No | 61 |
| 7 | 59 | M | 3 | IT MTX,WBI | 2 | Yes | 47 |
| 8 | 59 | M | 2 | IT MTX,WBI, VP shunt | 1 | Yes | 532 |
| 9 | 66 | F | 4 | IT MTX,WBI, VP shunt | 3 | No | 114 |
| 10 | 59 | M | 2 | IT MTX,WBI, VP shunt | 2 | Yes | 104 |

[a] At the time intrathecal methotrexate was finished (intrathecal methotrexate alone cases) or WBI was finished

*IT MTX* intrathecal methotrexate

## Toxicities

The worst grades of toxicity in each patient during the intrathecal methotrexate therapy and WBI are summarized in Table 3. Grade 3 or 4 neutropenia was observed in two patients and grade 3 or 4 leukopenia in three patients. All of the grade 3 adverse events, namely headache, nausea and appetite loss, were observed at the beginning of the treatment. The main non-hematological adverse events that appeared anew after the beginning of the treatment were headache (2 cases), nausea (2 cases), vomiting (2 cases), and general fatigue (1 cases). All of these adverse events were grade 1 in severity, except for headache, which was grade 2 in severity. Early death within 30 days of the last administration of intrathecal methotrexate occurred in five patients, of whom one patient who developed grade 4 neutropenia, leukopenia and febrile neutropenia died on the day following the last intrathecal methotrexate administration. The major complications caused by VP shunt were not observed.

## Efficacy

The treatment and clinical outcomes of the 10 patients who received treatment are summarized in Table 4. RTOG-NFC improvement was obtained in 6 (60%) patients, 5 of whom and another patient could leave the hospital temporarily (Table 4). All the patients had died by the time of this analysis. One patient was considered to have died a treatment-related death, 1 died from progression of peritoneal dissemination, and all of the remaining 10 patients died from the progression of the LMC. The median overall survival time from the diagnosis of LMC was 60 days in the 12 patients (Fig. 2), but 90 days in those who had received any treatment for LMC. The RTOG-NFC class did not become worse with VP shunt in any of the 3

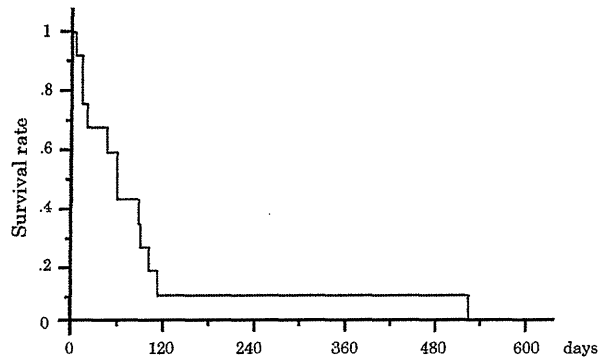


**Fig. 2** Overall survival from the diagnosis of LMC

patients in whom VP shunt was performed, and 1 patient in whom ITC, WBI, and VP shunt were administered survived for a considerably long period of 532 days.

## Discussion

Although cancer cells may seed the leptomeninges in patients with any type of solid tumors, the highest incidence of LMC has been reported in breast and lung cancer patients (12–34 and 10–26%, respectively); the incidence of LMC complicating gastrointestinal tract cancer is comparatively low (4–14%) [11]. Recently, the advances in systemic chemotherapy brought about by the development of new agents, including molecular-targeted agents, has contributed to a longer survival of cancer patients than that in the twentieth century. The median survival time of advanced gastric cancer patients treated by systemic chemotherapy has exceeded one year. In this retrospective study, the median interval between the initial diagnosis of gastric cancer and development of LMC was 15.6 months. Thus, it is anticipated that the incidence of LMC complicating gastric cancer will increase along with the prolonged survival brought by the advances in systemic chemotherapy.

In this study, the histological type of the tumor in 10 of the 12 patients (83%) was poorly differentiated adenocarcinoma or signet-ring cell carcinoma. This result is consistent with that suggested by previous reports. The majority of gastric cancer patients with LMC have poorly differentiated or signet-ring cell cancer [3, 4, 12]. In the diffuse type of gastric cancer, peritoneal dissemination and lymph node metastasis appear to be the major metastatic sites. Thus, the most frequent sites of concurrent metastasis associated with LMC in patients with gastric cancer were lymph node metastasis and peritoneal dissemination, as corroborated by both this study and previous reports [13].

Once LMC develops, irrespective of the primary cancer site, depressed neurological functions and neurological deficits cause reduction in the activities of daily living and extreme deterioration of the quality of life, and the prognosis is very poor. Because systemic chemotherapy is not effective against LMC, intraventricular chemotherapy and/or radiation have been most commonly employed for its treatment. Although no novel administration method of intrathecal methotrexate has been established, use of a low dose and daily intraventricular administration of methotrexate have been reported to be associated with reduced neurotoxicity [14]. Notwithstanding this treatment, the overall median survival of LMC patients was as low as 0.7–5.8 months [15–17]. In the largest case series of 90 patients with LMC complicating various kinds of cancers at the Memorial Sloan-Kettering Cancer Center who received focal irradiation and intraventricular methotrexate from 1975 to 1980, the overall median survival was reported to be 5.8 months [17]. However, breast cancer (46 patients) was the most commonly documented primary tumor in that study, and no gastric cancer patients were included in the report. As for the breast cancer patients in the case series, 28 patients (61%) showed symptomatic improvement or stabilization, and their overall median survival was 7.2 months. Consistent with the prognosis of LMC complicating gastric cancer being much worse, with an overall median survival ranging from 4 to 6–7 weeks [3, 4], the median overall survival of the 12 patients was about nine weeks (60 days) in our present study. Thus, establishment of an effective treatment strategy for LMC complicating gastric cancer is warranted.

Omuro et al. [9] reported that VP shunt resulted in improvement of the symptoms of intracranial hypertension in 27 (77%) of the 37 patients with LMC. In our study, the treatment strategy changed with the passage of time and accumulation of experience, and VP shunt was applied to the last three patients, one of whom survived for a considerably long period of 532 days. Retrospectively, among the five patients who were actually treated with the two modalities of intraventricular methotrexate plus WBI, two patients would have fulfilled the eligibility criteria for VP shunt; the survival times of these two patients were as short as 61 and 47 days. This study had its limitations, e.g., the small sample size of the study population and the retrospective study design; nonetheless, the results suggest that VP shunt may have potential clinical benefit for selected gastric cancer patients with complicating LMC. Ideally, the survival benefit of VP shunt should be evaluated in future clinical trials, although most patients with LMC are generally poor candidates for clinical trials.

The goals of treatment of LMC include not only prolongation of survival, but also improvement of the neurological symptoms. ITC and/or WBI have been tried in the palliative setting for selected patients. Lee et al. [3] reported that incomplete resolution of neurological symptoms was observed in only one among the 10 patients who

received ITC, and five patients showed no significant changes in clinical symptoms. Once LMC is diagnosed in gastric cancer patients, immediate hospitalization is indicated, because of the severe neurological symptoms. In this study, improvement of RTOG-NFC was seen in 2 of 3 patients by ITC and 4 of 7 by ITC followed by WBI. It is considered a very significant result that 6 of the 10 patients who received multidisciplinary treatment could temporarily leave the hospital.

In conclusion, this study suggests that ITC might be effective for obtaining improvement of neurological functions, and further accumulation of clinical experience is necessary to evaluate the efficacy of multidisciplinary treatment, including WBI and VP shunt.

**Conflict of interest** No author has any conflict of interest.

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# Modified FOLFOX-6 Therapy for Heavily Pretreated Advanced Gastric Cancer Refractory to Fluorouracil, Irinotecan, Cisplatin and Taxanes: A Retrospective Study

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**Objective:** Since 2007, S-1 plus cisplatin therapy has been recognized as the standard first-line treatment for advanced gastric cancer in Japan. However, no standard regimen has been established for patients refractory to first-line treatment. Furthermore, irinotecan and paclitaxel are considered key drugs for second-line treatment. Several studies have investigated the efficacy and tolerability of combination therapy with oxaliplatin, 5-fluorouracil and leucovorin (modified FOLFOX-6) for advanced gastric cancer. Here, we examined the efficacy and toxicity of modified FOLFOX-6 therapy in heavily pretreated patients with advanced gastric cancer refractory to 5-fluorouracil, irinotecan, cisplatin and taxanes.

**Methods:** Fourteen patients with advanced gastric cancer refractory to 5-fluorouracil, irinotecan, cisplatin and taxanes were included in the study. In modified FOLFOX-6 therapy, 85 mg/m$^2$ oxaliplatin, 400 mg/m$^2$ 5-fluorouracil and 200 mg/m$^2$ leucovorin on Day 1 were administered biweekly by intravenous infusion, followed by the administration of 2400 mg/m$^2$ 5-fluorouracil by a 46-h continuous infusion.

**Results:** The median age of the patients was 59 years (range, 22–74). A median of 5.5 (range, 1–13) chemotherapy cycles were administered. The overall response rate was 23.1% in patients with measurable lesions. Of the 12 patients with advanced gastric cancer refractory to cisplatin, 2 showed partial response (response rate, 18.2%). The progression-free survival was 90 days, and the median survival time from the initiation of modified FOLFOX-6 therapy was 268 days. Grade 3–4 toxicities most commonly observed included neutropenia (57%), anaemia (14%), thrombocytopenia (21%) and hyperammonaemia (7%).

**Conclusions:** Modified FOLFOX-6 therapy in patients refractory to 5-fluorouracil, irinotecan, cisplatin and taxanes may be a potential advanced gastric cancer therapeutic strategy.

*Key words: advanced gastric cancer – FOLFOX – salvage therapy*

## INTRODUCTION

Gastric cancer is the second leading cause of death from cancer worldwide and is the most common cancer in Japan (1). Early diagnosis of gastric cancer has improved the survival rate of patients with gastric cancer, while prognosis of advanced gastric cancer (AGC) remains poor. The main treatment for AGC is chemotherapy (2,3). However, a worldwide consensus on standard chemotherapy regimens has yet to be established. Two phase III studies assessing chemotherapy regimens were conducted in Japan in 2007. One was the JCOG 9912 trial, which revealed the non-inferiority of S-1 alone to 5-fluorouracil (5-FU) alone and failed to demonstrate the superiority of irinotecan plus cisplatin to 5-FU alone in terms of overall survival (OS) (4). This trial concluded that S-1 alone should be considered as a potential standard chemotherapy for AGC. The SPIRITS trial demonstrated the superiority of S-1 plus cisplatin to S-1 alone in terms of OS (5). On the basis of the results of these trials, S-1 plus cisplatin was established as the standard first-line treatment for AGC in Japan. However, no standard chemotherapy regimen has been established for patients refractory to first-line chemotherapy. For patients refractory to the S-1 + cisplatin therapy, irinotecan and paclitaxel are considered to be the key drugs following the first relapse or refractory disease (6,7).

Oxaliplatin may also be a promising therapeutic drug for the treatment of AGC. It is a third-generation platinum compound that was developed with an improved tolerability and efficacy compared with cisplatin (8,9). It has shown activity in many tumour cell lines resistant to cisplatin (10). The superiority of oxaliplatin-based regimens to cisplatin-based regimens was demonstrated in the Revised European-American Lymphoma-2 phase III study (11). Furthermore, the results of a phase III study comparing 5-FU/leucovorin (LV)/cisplatin with 5-FU/LV/oxaliplatin showed that oxaliplatin was at least as effective as cisplatin (12). In a phase II study conducted in Japan, Koizumi et al. (13) demonstrated the feasibility and efficacy of S-1 + oxaliplatin for chemo-naïve patients with AGC. Oxaliplatin combined with 5-FU has synergistic activity (14). Bolus and continuous infusions of 5-FU, LV and oxaliplatin (FOLFOX) improved the survival rate of patients with metastatic colorectal cancer (15–17).

Moreover, several studies suggest that modified FOLFOX-6 (mFOLFOX-6) may be effective in patients with gastric cancer (18–21). Louvet et al. conducted a phase II study of mFOLFOX-6 in patients with AGC and demonstrated an overall response rate of 44.9%, a median progression-free survival (PFS) of 6.2 months and a median OS of 8.6 months (18). Several recent studies suggest that FOLFOX therapy may be effective as a salvage therapy for AGC (22–25). However, no clinical trial has investigated the effect of mFOLFOX-6 in heavily pretreated patients with AGC. In our study, we retrospectively investigated the efficacy and safety of mFOLFOX-6 therapy in patients with AGC refractory to 5-FU, irinotecan, cisplatin and taxanes.

## PATIENTS AND METHODS

### Patients

Twenty-five patients with AGC received mFOLFOX-6 therapy between December 2005 and November 2010 at the Shizuoka Cancer Center, Shizuoka, Japan. The inclusion criteria were as follows: (i) age >20 and <75 years; (ii) an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2; (iii) adequate major organ functions; (iv) no other cancer and no serious complications, such as active infectious disease and serious heart disease; and (v) disease refractory to 5-FU, irinotecan, cisplatin and taxanes. Patients were excluded if they had unresolved bowel obstruction, central nervous system metastases and mental disease. Eleven patients were excluded, as their disease was not refractory or they had been cases of failure to all the 4 key drugs.

### Treatment

The treatment consisted in the administration of 85 mg/m$^2$ oxaliplatin and 200 mg/m$^2$ LV by a 2-h intravenous infusion, followed by the administration of 400 mg/m$^2$ bolus 5-FU and 2400 mg/m$^2$ 5-FU by a 46-h continuous infusion. The treatment was repeated every 2 weeks until disappearance of disease progression, appearance of unacceptable toxicities or patient refusal. In the event of serious haematological toxicities, the treatment was suspended until recovery.

### Response and Toxicity Evaluation

Patient characteristics, adverse events, treatment compliance, treatment response, PFS and OS were analysed retrospectively with the data collected from medical records. The response was assessed every 2 months by computed tomography. Objective responses in measurable metastatic lesions were evaluated according to the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST ver.1.1). The survival time was calculated from the initiation of mFOLFOX-6 therapy until death or last confirmation of survival. Symptomatic toxicity and laboratory data were monitored every week at the outpatient clinic. The toxicity was evaluated according to the Common Toxicity Criteria for Adverse Events, version 4.0.

## RESULTS

### Patient Characteristics

Patient characteristics are shown in Table 1. Fourteen patients met the inclusion criteria. The median age was 59 years (range, 22–74 years), and majority of the patients were males (79%). Twelve patients (86%) showed an ECOG PS score of 0 or 1. Eight patients (57%) had primary lesions and five (36%) had ascites. Metastatic sites included the

**Table 1.** Patient characteristics

| | Number of patients |
|---|---|
| Age | |
| Median (range) years | 59 (22–74) years |
| Sex | |
| Male | 11 |
| Female | 3 |
| ECOG PS | |
| 0 | 4 |
| 1 | 8 |
| 2 | 2 |
| Disease status | |
| Metastatic | 8 |
| Recurrent | 6 |
| Ascites | |
| Yes | 5 |
| No | 9 |
| Site of metastasis | |
| Liver | 8 |
| Lymph nodes | 8 |
| Peritoneal carcinomatosis | 3 |
| Lung | 2 |
| Other | 2 |
| No. of metastatic sites | |
| 1 | 6 |
| 2 | 6 |
| ≧3 | 2 |
| Prior chemotherapy line | |
| Three | 6 |
| Four | 7 |
| Five | 1 |
| Prior chemotherapy drugs | |
| Fluoropyrimidines | 10 |
| Fluoropyrimidines + cisplatin | 7 |
| Irinotecan + cisplatin | 8 |
| Irinotecan | 7 |
| Taxanes | 15 |
| Other | 3 |
| Response of cisplatin-based regimens | |
| Complete response | 0 |
| Partial response | 9 |
| Stable disease | 1 |
| Progressive disease | 3 |

ECOG PS, Eastern Cooperative Oncology Group performance status.

liver (57%), peritoneum (21%), lung (14%) and abdominal lymph nodes (57%).

The data on previous chemotherapy are shown in Table 1. Eight patients (57%) received mFOLFOX-6 as more than their fifth-line treatment. The previous therapy consisted in the administration of fluoropyrimidines plus cisplatin in seven patients and irinotecan plus cisplatin in eight. Twelve patients with AGC were refractory to cisplatin. A median of 5.5 (range, 2–12) chemotherapy cycles of previous cisplatin-based therapy were administered with a median total dose of 375 mg/m$^2$. The response rate of the previous cisplatin-based therapy was 69.2% (9 of 13).

### Dose Intensity

The median number of chemotherapy cycles of oxaliplatin, 5-FU bolus infusion and 5-FU continuous infusion were similar (median, 5; range, 1–13). The dose intensity of oxaliplatin was calculated as 35 mg/m$^2$/week, which corresponded to 82% of the planned dose. The dose intensity and the planned dose received for 5-FU bolus infusion and 5-FU continuous infusion were 158 mg/m$^2$/week and 79% and 1020 mg/m$^2$/week and 85%, respectively.

### Toxicity

The observed haematological and non-haematological toxicities are shown in Table 2. Haematological toxicities were common, with eight patients (57%) experiencing grade 3 or 4 neutropenia, two (14%) experiencing grade 3 anaemia and

**Table 2.** Incidence of haematological and non-haematological toxicities

| Type of toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Haematological | | | | |
| Leukopenia | 0 | 4 | 5 | 1 |
| Neutropenia | 1 | 2 | 4 | 4 |
| Anaemia | 2 | 1 | 2 | 0 |
| Thrombocytopenia | 1 | 1 | 1 | 2 |
| Febrile neutropenia | — | — | 0 | 0 |
| Non-haematological | | | | |
| Anorexia | 8 | 5 | 0 | 0 |
| Malaise | 4 | 6 | — | — |
| Nausea | 8 | 1 | 0 | — |
| Vomiting | 2 | 0 | 0 | 0 |
| Peripheral neuropathy | 4 | 2 | 0 | 0 |
| Diarrhoea | 3 | 0 | 0 | 0 |
| Mucositis oral | 1 | 2 | 0 | 0 |
| Watering eyes | 0 | 1 | 0 | — |
| Creatinine increased | 0 | 0 | 0 | 0 |
| Hepatic failure | — | — | 0 | 1 |

three (24%) experiencing grade 3 or 4 thrombocytopenia. One patient (7%) experienced grade 4 hepatic failure due to hyperammonaemia. No patient died within 30 days of the last administration of mFOLFOX-6 therapy.

### Response and Survival

Response was evaluated among 13 patients who had measurable lesions. Overall, three patients had a partial response. The response rate was 23.1% (3 of 13) with a disease control rate (partial response + stable disease) of 53.8% (7 of 13) according to RECIST ver1.1. The median follow-up period was 362 days as of December 2010. The median OS was 268 days after initiation of mFOLFOX-6 therapy (Fig. 1). The median PFS was 90 days (Fig. 2). Six patients (42.9%) refractory to mFOLFOX-6 therapy received the following subsequent chemotherapies: two patients received fluoropyrimidine-based therapy, one received irinotecan plus taxane-based therapy, two received taxanes and five received other therapies.

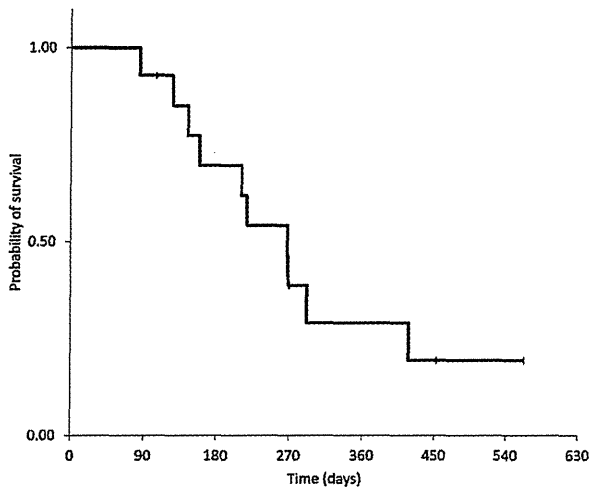


**Figure 1.** Overall survival.

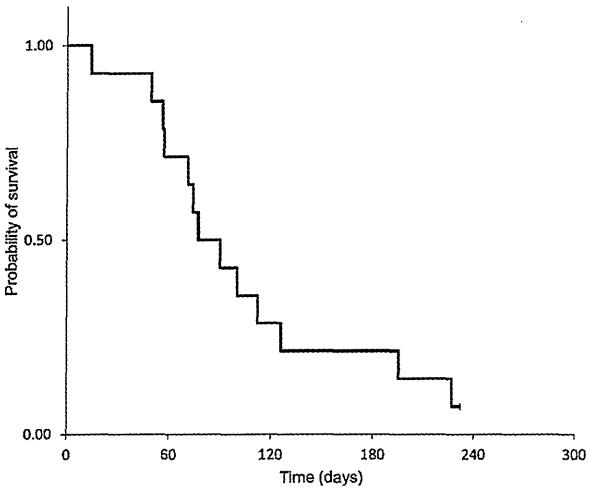


**Figure 2.** Progression-free survival.

## DISCUSSION

The results reported here are similar to those of previous studies. Recently, Kim et al. (22) showed that FOLFOX-4 may be effective as salvage therapy for patients with AGC. In their phase II study, FOLFOX-4 was primarily administered as second-line treatment for AGC, and their study demonstrated a response rate of 21%, a median PFS of 3.0 months and a median OS of 6.2 months. By comparison, the results of our study, in which all the patients received three or more lines of treatment with 5-FU, irinotecan, cisplatin and taxanes, demonstrated a response rate of 23%, a median PFS of 3.0 months and a median OS of 8.9 months. On the basis of the similarity of our findings to those of other studies, we speculate that mFOLFOX-6 therapy may have consistent efficacy, irrespective of the type of previous chemotherapy (Table 3).

mFOLFOX-6 therapy may also be effective in previously platinum-treated patients with AGC. For example, a phase II study of mFOLFOX-6 in previously platinum-treated patients with AGC demonstrated a response rate of 26%, a median PFS of 4.3 months and a median OS of 7.3 months (23). In our study, 11 patients refractory to cisplatin and assessable for response demonstrated a response rate of 18% (2/11), a median PFS of 3.0 months and a median OS of 8.9 months. These findings suggest that mFOLFOX-6 therapy is effective in previously platinum-treated patients with AGC and that oxaliplatin has no cross-resistance with cisplatin.

The most common toxicity in our study was neutropenia. We observed grade 3–4 haematologic neutropenia in 57% of patients, anaemia in 14% and thrombocytopenia in 21%. Seo et al. (25) reported grade 3–4 neutropenia only 1 in 5% of patients receiving FOLFOX therapy as second-line treatment for AGC. One reason for the increased neutropenia in our study is that our patients were previously heavily pretreated and eight patients (57%) received mFOLFOX-6 therapy as a fifth- or sixth-line treatment. Furthermore, mFOLFOX-6 provoked hyperammonaemia in one patient in our study. Several previous studies have identified 5-FU-induced hyperammonaemia after chemotherapy. The dose of 5-FU continuous infusion in mFOLFOX-6 therapy is higher than that in FOLFOX-4 therapy. Shoji et al. (26) suggested a change from mFOLFOX-6 therapy to FOLFOX-4 therapy to prevent hyperammonaemia. In our study, the patient immediately recovered from hyperammonaemia after mFOLFOX-6 therapy was terminated; however, the reason for hyperammonaemia remains unclear.

In conclusion, mFOLFOX-6 therapy after failure of therapy with 5-FU, irinotecan, cisplatin and taxanes may be considered a therapeutic strategy for AGC. But the number

**Table 3.** Comparison of the results with those of previous studies of FOLFOX therapy as salvage therapy for advanced gastric cancer (ACG)

| Study | | Line | Number of patients | RR (%) | Median PFS (months) | Median OS (months) | NCI-CTC ≧ Grade 3 Neutropenia (%) |
|---|---|---|---|---|---|---|---|
| This report | Retro | 4th–6th | 14 | 23 | 3.0 | 8.9 | 57 |
| Kim et al. (21) | P‖ | 2nd–4th | 42 | 21 | 3.0 | 6.2 | 40 |
| Kim et al. (22) | P‖ | 2nd | 26 | 26 | 4.3 | 7.3 | — |
| Suh et al. (23) | P‖ | 2nd– | 33 | 27 | 3.5 | 7.9 | 45 |
| Seo et al. (24) | Retro | 2nd– | 62 | 22.6 | 3.0 | 8.0 | 14.5 |

RR, response rate; PFS, progression-free survival; OS, overall survival; NCI-CTC, National Cancer Institute – Common Toxicity Criteria.

of subjects in our study is small, in addition to it being a study with retrospective observation.

Further prospective studies are warranted to confirm the efficacy and safety of this AGC therapeutic strategy.

## Conflict of interest statement

There is no financial support or relationship that may pose a conflict of interest.

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# Survival Benefit of Palliative Gastrectomy in Gastric Cancer Patients with Peritoneal Metastasis

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**Abstract**
*Background* The survival benefit of palliative gastrectomy in patients with peritoneal metastasis as a single incurable factor remains unclear.
*Methods* A total of 148 gastric cancer patients with peritoneal metastasis underwent gastrectomy or chemotherapy at the Shizuoka Cancer Center between September 2002 and December 2008 and were included in this study. The effects of gastrectomy and chemotherapy on their long-term outcome were investigated. Multivariate analysis was also performed to identify independent prognostic factors.
*Results* Gastrectomy was performed in 82 patients and subsequent chemotherapy was administered to 55. Chemotherapy was selected as an initial treatment for 66 patients. Median survival time (MST) was identical between patients with and without gastrectomy (13.1 vs. 12.0 months; $P = 0.410$). Conversely, MST was significantly longer in patients who received chemotherapy (13.7 months) than those who did not (7.1 months; $P = 0.048$). According to the results of multivariate analysis, chemotherapy (hazards ratio [HR] = 0.476; 95 % CI = 0.288–0.787) was selected as an independent prognostic factor, while gastrectomy was not.
*Conclusions* The results of the present study did not show a survival benefit of palliative gastrectomy in selected patients with peritoneal metastasis. Instead, chemotherapy has to be considered as an initial treatment for these patients.

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## Introduction

Gastric cancer is diagnosed frequently and is the second leading cause of cancer-related deaths in Japan [1]. Although the long-term outcome of early gastric cancer is good, that of advanced gastric cancer is dismal, particularly when combined with other incurable factors [2–4]. Recent advances in chemotherapy have improved the survival rate of gastric cancer patients with incurable factors. However, survival rates remain limited and there is still room for improvement in the survival rate [5, 6].

The incurable factors observed frequently in patients with advanced gastric cancer are peritoneal, liver, and distant lymph node metastases [7, 8]. Better survival rates were reported in Japan following gastrectomy plus metastasectomy if the incurable factors were liver or para-aortic lymph node metastases and if the surgery was curative [9–12]. In contrast, curative resections are difficult in patients with widespread peritoneal metastasis, which is the most frequently observed incurable factor [13–16]. Although a few surgeons have reported the efficacy of performing a peritonectomy, this concept has not been accepted widely, even in Japan [17].

Previously, a number of authors investigated the feasibility of palliative gastrectomy in patients with incurable factors [14, 18–24]. However, each study included patients with a range of incurable factors; therefore, the effect of gastrectomy in selected patients with peritoneal metastasis remains unclear. The aim of the present study was to clarify the effects of gastrectomy on gastric cancer patients

with peritoneal metastasis. The appropriate treatment strategy in patients with localized peritoneal metastasis was also investigated.

## Materials and methods

### Patients

Between September 2002 and December 2008, 279 gastric cancer patients with peritoneal metastasis underwent gastrectomy or chemotherapy at the Shizuoka Cancer Center, Japan. Of these, 131 patients had incurable factors other than peritoneal metastasis so the remaining 148 patients with no other obvious incurable factors were included in this study. Pathological examination of biopsy specimens from the stomach revealed adenocarcinoma in all patients. Patients who had received any previous treatment for gastric cancer were not included in the present study. Peritoneal metastasis was diagnosed histopathologically in patients who underwent laparotomy (106 patients) or was diagnosed clinically using computed tomography in patients who did not undergo laparotomy (42 patients).

The patients' characteristics and surgical and pathological findings were collected retrospectively from our prospectively recorded database and individual patient records. The patients' clinicopathological characteristics were analyzed, and survival curves were compared according to the treatment modalities administered (gastrectomy and chemotherapy). Multivariate analysis was also conducted to identify independent prognostic factors.

This study followed ethical guidelines for human subjects and was approved by the institutional review board of the Shizuoka Cancer Center.

### Pretreatment examinations

Computed tomography (CT) with contrast medium was performed as a routine pretreatment examination in all patients except those with poor renal function or with an allergy to the contrast medium. Patients were regarded as having clinically evident peritoneal metastasis (cP+) if the CT findings showed obvious peritoneal metastasis which included massive ascites, cirrhosal implants of the intra-abdominal area or on the small or large bowel, remarkably increased visceral fat density, and omental metastasis. If CT did not show any obvious peritoneal metastasis, patients were regarded as not having clinically evident peritoneal metastasis (cP−).

Macroscopic type was classified according to the Japanese Gastric Cancer Association (JGCA) classification system [25]. Histological type was also classified according to the JGCA classification system, in which tubular and papillary adenocarcinoma are defined as differentiated adenocarcinoma, while poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma are defined as undifferentiated adenocarcinoma.

The degree of peritoneal metastasis was classified in patients who underwent laparotomy as follows: P0, no implants to the peritoneum; P1, cancerous implants to the region directly adjacent to the stomach peritoneum (above the transverse colon), including the greater omentum; P2, several scattered metastases to the distant peritoneum and ovarian metastasis alone; and P3, numerous metastases to the distant peritoneum [26].

### Indications for gastrectomy

In patients with P1, gastrectomy was performed if macroscopic curative resection was expected. Gastrectomy was also selected as an initial treatment in patients with tumor-associated symptoms such as bleeding or gastric outlet obstruction even if curative resection could not be expected. If patients had P2 or P3 peritoneal metastasis and they did not have tumor-associated symptoms, gastrectomy would not be performed in principle.

### Statistics

All continuous data are presented as the median (range). Survival rates were calculated using the Kaplan–Meier method, and the log-rank test was used to compare the groups. In this study, overall survival time was defined as time from initial treatment (surgery or chemotherapy) to any death, including noncancer-related death.

Independent prognostic factors were identified using the Cox proportional hazards model. In the analysis, each patient's age ($<60$ or $\geq 60$ years old), sex, clinically evident peritoneal metastasis (cP− or cP+), gastrectomy (performed or not performed), chemotherapy (received or not received), Eastern Cooperative Oncology Group (ECOG) performance status (0, 1 or 2, 3), macroscopic type (type 4 or other), and histology (differentiated or undifferentiated) were included as covariates. The Bonferroni test was used during multiple comparisons. A $P$ value $<0.05$ was considered significant. All statistical analyses were conducted using *R* version 2.13.1.

## Results

The patient characteristics are indicated in Table 1. Macroscopic type 3 tumors were observed in 43 % of the patients and type 4 tumors were observed in 39 %. Tumors were undifferentiated in three-fourths of the patients. The pretreatment ECOG performance status was generally good

(≤1) and was 2 or higher in 10 % of patients. Gastrectomy was performed in 82 patients and subsequent chemotherapy was administered to 55 of these patients. Chemotherapy was selected as an initial treatment in 66 patients. We also compared the background data between patients according to the treatment provided. There were no differences between any two groups with respect to sex, ECOG performance status, histology, and macroscopic type. The median age was significantly different between the groups, with patients who received gastrectomy only the oldest followed by patients who received both gastrectomy and chemotherapy. The incidence of clinically evident peritoneal metastasis was significantly higher in patients who underwent chemotherapy only than in those who underwent gastrectomy only or both gastrectomy and chemotherapy.

Table 2 lists the treatments provided. Of the 82 patients who underwent gastrectomy, total gastrectomy was performed more frequently (67 %) than distal gastrectomy (33 %). S1-based chemotherapy was the most frequently selected treatment regimen in this study. Of 121 patients who received chemotherapy, second-line chemotherapy was given in 64 % of patients and third-line chemotherapy was administered in 35 % of patients.

Figure 1 shows the overall survival curve of all patients. Of the 148 patients, 137 were followed until their death. Median follow-up period of survivors was 29.7 months. One-year and three-year overall survival rates were 53.9 and 18.1 %, respectively. Figure 2a shows the overall survival curves of patients with and without gastrectomy. The median survival time (MST) of patients with gastrectomy was 13.1 months ($n = 82$) and that without gastrectomy was 12.0 months ($n = 66$; $P = 0.410$). Overall survival curves of patients who did or did not receive chemotherapy are shown in Fig. 2b. MST was significantly longer in patients who received chemotherapy (13.7 months; $n = 121$) than in those who did not (7.1 months; $n = 27$; $P = 0.048$).

Table 3 shows the results of the Cox proportional hazards model. Chemotherapy [hazards ratio (HR) = 0.476; 95 % CI = 0.288–0.787], ECOG performance status 0 or 1(HR = 0.278; 95 % CI = 0.156–0.495), and macroscopic tumor types other than type 4 (HR = 0.566; 95 % CI = 0.377–0.848) were selected as independent prognostic factors, while gastrectomy was not selected.

**Table 1** Patient characteristics

| | | Gastrectomy | Chemotherapy | Gastrectomy + chemotherapy |
|---|---|---|---|---|
| Number (*n*) | 148 | 27 | 66 | 55 |
| Age (years)[a] | 65 (20–85) | 77 (53–85) | 60 (20–77) | 67 (34–76) |
| Sex (*n*) | | | | |
| Male | 90 | 18 | 36 | 36 |
| Female | 58 | 9 | 30 | 19 |
| Performance status (*n*) | | | | |
| 0 or 1 | 133 | 23 | 58 | 52 |
| 2 or 3 | 15 | 4 | 8 | 3 |
| Histology (*n*) | | | | |
| Differentiated | 36 | 7 | 20 | 9 |
| Undifferentiated | 112 | 20 | 46 | 46 |
| Macroscopic type (*n*) | | | | |
| ≠type 4 | 90 | 19 | 35 | 36 |
| type 4 | 58 | 8 | 31 | 19 |
| Clinically evident peritoneal metastasis[b] | | | | |
| Yes (cP+) | 62 | 2 | 51 | 9 |
| No (cP) | 86 | 25 | 15 | 46 |
| Gastrectomy (*n*) | | | | |
| Yes | 82 | 27 | 0 | 55 |
| No | 66 | 0 | 66 | 0 |
| Chemotherapy (*n*) | | | | |
| Yes | 121 | 0 | 66 | 55 |
| No | 27 | 27 | 0 | 0 |

[a] The differences between each group are statistically significant ($P < 0.0167$ between any two groups)

[b] The difference is statistically significant between patients who underwent chemotherapy and those who underwent gastrectomy. It is also statistically significant between patients who underwent chemotherapy and those who underwent gastrectomy + chemotherapy