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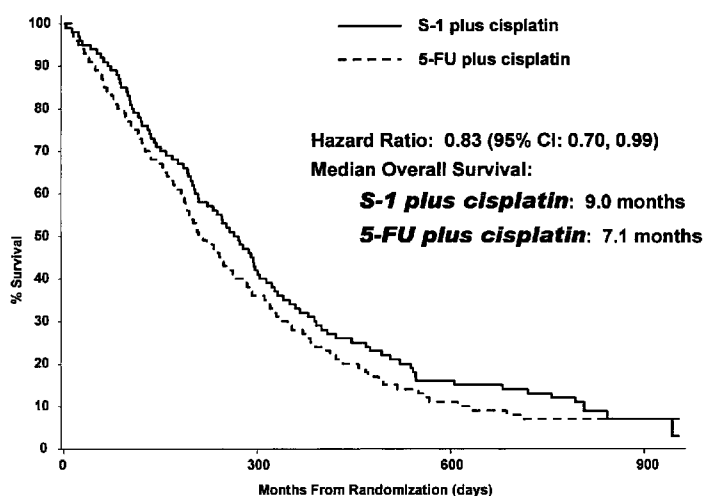
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(54) Title: TREATMENT OF DIFFUSE-TYPE GASTRIC CANCERS USING S-1 AND CISPLATIN

[Fig. 1]



(57) Abstract: The present invention provides an improved method for treating diffuse-type gastric cancer or a mixed-type gastric cancer, including advanced diffuse-type and mixed type gastric cancer and metastatic diffuse-type and mixed-type gastric cancer, by administering S-1 and cisplatin to patients in need of treatment for diffuse-type gastric cancer or mixed type gastric cancer.

Description

Title of Invention: TREATMENT OF DIFFUSE-TYPE GASTRIC CANCERS USING S-1 AND CISPLATIN

5 Technical Field

The present invention relates to the treatment of gastric cancers using a combination therapy of S-1 and cisplatin. In particular, it relates to an improved method of treating patients with diffuse-type gastric cancer by administering S-1 and cisplatin to a patient in need of such treatment.

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Background Art

Gastric cancer is the fourth most common cancer worldwide, behind lung, breast, and colorectal cancers, and is the second most common cause of cancer-related deaths, with an estimate of 800,000 deaths annually (Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. CA Cancer J Clin 2008;58(2):71-96; Parkin DM Bray F, Ferlay J, Pisani P. Global Cancer Statistics, 2002. CA Cancer J Clin 2005;55(2):74-108). The incidence and mortality rates of gastric cancer vary greatly between regions. Over the past seven decades, these rates have decreased progressively in North America and Western Europe, but remain high in Eastern Europe, South America, and Asia (Levi F, Lucchini F, Gonzales Jr, Fernandez E, Negri E, La Vecchia C., "Monitoring Falls in Gastric Cancer Mortality in Europe." Ann Oncol 2004; 15:338-345). Although gastric cancer is less common in the United States than in many geographic regions, it is estimated that 21,500 new cases and 10,880 deaths from gastric cancer will occur in the United States in 2008 (Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murry T, et al. Cancer Statistics, 2008. CA Cancer J. Quinn. 2008; 58:71-96).

25 The histology of gastric cancer is an important prognostic factor in advanced gastric cancer. The World Health Organization (WHO) histopathological classification of gastric cancer differentiates by groups: well-differentiated, moderately-differentiated, poorly-differentiated, signet ring cell cancer, and mucinous-type. According to Lauren's classification, gastric cancer is divided into two categories: intestinal type, and diffuse type.

30 As used in the specification, unless otherwise specified, diffuse-type gastric cancer may be characterized by non-cohesive single or small nests of cells with little or no gland formation, carcinoma with solid sheets, tight clusters, and cords of cells being evident,

carcinoma with signet ring differentiation, small cell cancer with absent to minimal intracellular mucin, anaplastic cells with little intracellular mucin, or extracellular mucin with pure signet ring cell morphology. As used in the specification, unless otherwise specified, intestinal-type gastric cancer includes the pure intestinal-type gastric cancer based on Lauren's classification as well as the papillary, tubular, and part of mucinous histology described by the WHO classification. As used in the specification, unless otherwise specified, mixed-type gastric cancer includes tumors with histologic features of unclassified/indeterminate carcinoma under the Lauren classification, as well as mixed histology with a component of diffuse-type gastric cancer as described above and a component of intestinal-type gastric cancer as described above.

Recently published data indicate that the survival of patients with diffuse-type gastric cancer is significantly worse compared to those with intestinal type. Park et al. (2008) reviewed retrospectively medical records of 2,275 patients who underwent gastric resection. The overall cumulative five-year survival rates for these patients were 67% for intestinal type gastric cancer versus 54% for poorly-differentiated, or diffuse, gastric cancer. State-stratified analysis revealed that histologic type was not statistically related with stage 1, 2 or 3 disease; however, histologic type in patients with stage 4 disease was found to be statistically associated with survival (Park KM, Jang YJ, Kim JH, Park SS, Park SH, Kim SJ, et al. Gastric Cancer Histology: Clinicopathologic Characteristics and Prognostic Value. *J Surg Oncol.* 2008; 98:520-25). Patients with intestinal type stomach cancer had a significantly better survival than did those with diffuse type stomach cancer (64% vs. 42% of patients surviving, $p = 0.020$) (Lee KH, Lee JH, Cho JK, Kim TW, Kang YK, Lee JS et al. A Prospective Correlation of Laurén's Histological Classification of Stomach Cancer with Clinicopathological Findings Including DNA Flow Cytometry. *Pathol. Res. Pract.* 2001; 197: 223-29). It has also been found that patients with poorly-differentiated tumors have a shorter survival than patients with well-differentiated or moderately-differentiated tumors (Patel PR, Yao JC, Hess K, Schnirer I, Rashid A, Ajani JA. Effect of Timing of Metastasis/Disease Recurrence and Histological Differentiation on Survival Patients with Advanced Gastric Cancer. *Cancer.* 2007; 110; 2186-90; Adachi Y, Yasuda K, Inomata M, Sato K, Shiraishi N, Kitano S. Pathology and Prognosis of Gastric Carcinoma. *CANCER* 2000; 89 (7): 1418-24).

In general, 5-fluorouracil (5-FU) is the mainstay of combination chemotherapies developed and tested in advanced gastric cancer. In gastric cancer, 5-FU is administered via continuous intravenous infusion (CIV) over five to 21 days depending on the combination

chemotherapy. In addition, several combination chemotherapies have been developed and assessed in randomized studies: FAM (5-FU, doxorubicin, and mitomycin), EAP (etoposide, doxorubicin, cisplatin), FAMTX (5-FU, doxorubicin, methotrexate), CF (cisplatin, 5-FU), ELF (etoposide, 5-FU, leucopirin), ECF (epirubicin, cisplatin, 5-FU), and more recently some combinations with new cytotoxic drugs, including DCF (docetaxel, cisplatin, and 5-FU), IF (irinotecan, 5-FU), XP (capecitabine and cisplatin), and EOX (epirubicin, oxaliplatin, and capecitabine).

Despite these new drugs for the treatment of advanced disease, the median overall survival for patients with advanced gastric cancer remains about nine months, and current treatments induce toxicities that can impact the quality of life of these patients. New combination therapies with improved tolerability and improved safety profiles that generate greater convenience and ease of patient management are needed in this palliative setting.

Summary of Invention

In one aspect, the present invention relates to an improved method for treating a diffuse-type or a mixed-type gastric cancer in a patient in need of such treatment, which comprises (i) administering to the patient an effective amount of S-1 and (ii) administering to the patient an effective amount of cisplatin. S-1 is a 1:0.4:1 molar mixture of Tegafur to Gimeracil to Oteracil potassium, and is always dosed on the amount of tegafur in the S-1. Preferably, the S-1 is administered at least twice daily in a total daily amount of about 20 mg/m² to about 80 mg/m² of Tegafur in S-1. More preferably, the total daily amount of S-1 is initially administered in an amount of about 30 mg/m² to about 80 mg/m² of Tegafur in S-1, subject to possible reduction in the event of unwanted side effects. More preferably, the S-1 is initially administered at least twice daily in a total daily amount of about 50 mg/m² to about 70 mg/m² of Tegafur in S-1. Preferably, the doses of S-1 are provided in equal amounts. Such doses may be administered for about 7 to about 28 consecutive days within a period of about 14 to about 35 days. While the cisplatin may be administered once at any point in the about 14 to about 35 day period, it is typically more convenient to administer cisplatin on the first day or the eighth day the S-1 dose is administered. Preferably, S-1 may be administered for about 21 consecutive days in a period of about 28 days, particularly when the patient is a Caucasian patient, along with about 75 mg/m² of cisplatin, which is also administered once within the 28 day period. S-1 may be administered at least one hour before or one hour after a meal. S-1 is preferably administered perorally.

In a preferred embodiment, the cisplatin is administered intravenously. In a further preferred embodiment, the cisplatin is administered once in a period of about 28 to about 35 days. More preferably, cisplatin is administered once in a period of about 28 days. In another preferred embodiment the cisplatin is administered as a dose of about 50 mg/m² to about 100 mg/m². More preferably, the cisplatin is administered as a dose of about 60 mg/m² to about 80 mg/m².

The present invention can be used when the diffuse-type gastric cancer is an advanced diffuse-type gastric cancer, including when the advanced diffuse-type gastric cancer is a metastatic diffuse-type gastric cancer. Likewise, the present invention can be used when the mixed-type gastric cancer is an advanced mixed-type gastric cancer, including when the advanced mixed-type gastric cancer is a metastatic mixed-type gastric cancer.

In a further preferred embodiment, the method according to the present invention is a first line therapy, that is, the advanced diffuse-type gastric cancer or advanced mixed-type gastric cancer has not been previously treated with chemotherapy, except for neo-adjuvant or adjuvant chemotherapy. Preferably, the patient has not lost more than 10% of his or her baseline weight prior to the beginning of treatment.

Preferably, the present invention relates to a method for treating an advanced diffuse-type or mixed-type gastric cancer in a patient in need of such treatment which comprises (i) perorally administering to the patient S-1 in an amount of about 10 mg/m² to about 40 mg/m² of Tegafur in the S-1 twice daily at least one hour before or after a meal for about 7 to about 28 consecutive days within a period of about 14 to about 35 days, and (ii) intravenously administering to the patient about 50 mg/m² to about 100 mg/m² of cisplatin once in a period of about 28 to about 35 days. More preferably, the present invention relates to a method for treating an advanced diffuse-type gastric cancer or advanced mixed-type gastric cancer which has not been previously treated with chemotherapy in a patient in need of such treatment which comprises (i) perorally administering to the patient S-1 in an amount of about 15 mg/m² to about 40 mg/m² per dose of Tegafur in the S-1. Most preferably, the patient is administered the S-1 in an amount of about 25 mg/m² to about 35 mg/m² per dose of Tegafur in the S-1.

The present invention also relates to use of a combination of first preparation consisting of therapeutically effective amount of S-1, wherein said S-1 is a pharmaceutical composition containing Tegafur, Gimeracil, and Oteracil potassium at a molar ration of 1:0.4:1,

and second preparation containing therapeutically effective amount of cisplatin for preparation of medicament for the treatment of a diffuse-type gastric cancer or a mixed gastric cancer.

Further, the present invention relates to a kit for the treatment of a diffuse-type gastric cancer or a mixed gastric cancer, comprising a first preparation consisting of therapeutically effective amount of S-1, wherein said S-1 is a pharmaceutical composition containing Tegafur, Gimeracil, and Oteracil potassium at a molar ration of 1:0.4:1, and a second preparation containing therapeutically effective amount of cisplatin.

Furthermore, a combination of first preparation consisting of therapeutically effective amount of S-1, wherein said S-1 is a pharmaceutical composition containing Tegafur, Gimeracil, and Oteracil potassium at a molar ration of 1:0.4:1, and second preparation containing therapeutically effective amount of cisplatin for the treatment of a diffuse-type gastric cancer or a mixed gastric cancer.

Brief Description of the Drawings

Figure 1 shows the difference in the overall survival in patients with diffuse-type of advanced gastric cancer and a limited number of patients with mucinous-type gastric cancer when treated with S-1/cisplatin as compared with the overall survival in patients with diffuse-type of advanced gastric cancer when treated with 5-FU/cisplatin.

Figure 2 shows the difference between overall survival in patients with metastatic disease/diffuse-type of advanced gastric cancer and a limited number of patients with mucinous-type gastric cancer, and less than 10% baseline weight loss when treated with S-1/cisplatin as opposed to when treated with 5-FU/cisplatin.

Description of Embodiments

S-1 is an oral fluoropyrimidine that combines Tegafur (FT), which is an oral prodrug of 5-FU, with two modulators, Gimeracil (CDHP), which inhibits 5-FU degradation by DPD inhibition, and Oteracil potassium (Oxo), which inhibits 5-FU phosphorylation in the digestive tract. S-1 is a fixed combination in a 1:0.4:1 molar ratio of Tegafur to Gimeracil to Oteracil potassium. S-1 is generally administered perorally. S-1 is more fully described in U.S. Patent Application 2008/0166427, the entirety of which is herein incorporated by reference.

S-1 is rationally designed to achieve an enhanced anti-tumor effect while decreasing adverse events. Tegafur is retained in blood for long periods of time when

administered orally and is gradually converted into 5-FU in the presence of CYP 2A6 (CYP = cytochrome p450 enzymes that are involved in metabolism in various drugs). Therefore it seems likely that higher blood levels of 5-FU would be obtained by oral administration of Tegafur than by oral or IV administration of 5-FU itself.

5 In practice, however, after an oral dose of Tegafur, 5-FU blood levels are lower than expected due to biodegradation by DPD in the liver. It was postulated that the combination of Tegafur with a powerful DPD inhibitor, such as Gimeracil, may achieve high blood 5-FU levels for long periods at relatively low Tegafur dose levels. This combination would result in increased anti-tumor activity, by reducing FBAL concentration, also result in decreased toxicities
10 thought to be associated with this metabolite. In addition, it was postulated that Oteracil potassium, an inhibitor of orotate phosphoribosyltransferase, the enzyme responsible for 5-FU phosphorylation in the gastro-intestinal tract, would reduce gastro-intestinal toxicity.

S-1 has undergone Phase 1 and early Phase 2 evaluation in Japan. In the initial Phase 1 study, S-1 was investigated as an oral agent for once daily administration. Single dose
15 administration in the range of 25 to 200 mg (as Tegafur) has been studied. S-1 was investigated at a schedule in which the drug was given twice daily for 28 days, followed by 2 weeks recovery. 6 of 11 patients (2 of whom had gastric cancer) were reported to experience tumor reduction at all dose levels studied (50 to 100 mg). Thus far, Phase 2 studies have been performed in patients with advanced gastric cancer at 50 mg and 75 mg of S-1 per patient. The overall response (by
20 modified World Health Organisation (WHO) criteria) rate reported in 28 patients with advanced gastric cancer was 53.6%; while in 30 patients with metastatic colorectal cancer, the overall response rate was 16.7% (13 of 30 colorectal patients had received previous treatment with a fluorinated pyrimidine). Overall, approximately 800 patients were enrolled in the Phase 1, early Phase 2, late Phase 2, and PK studies in Japan.

25 Based on the results of the Japanese clinical program, a clinical program to evaluate S-1 was initiated in the United States of America (USA) and Europe (EU) in the mid to late 1990s. The dosing regimen and schedule of administration used in these studies were similar to that approved in Japan. S-1 was administered orally twice a day in doses of up to 60 mg/m²/day of S-1 for up to 28 consecutive days, followed by a 7-day recovery period.
30 Antitumor activity was demonstrated and the results were consistent with those seen in the Japanese studies. However, unexpectedly higher toxicity was seen in the USA/EU studies as compared with the Japanese studies.

A possible explanation for the differences in toxicity reported in the Japanese studies as compared with the USA/EU studies could be the potential differences in the conversion rate of Tegafur to 5-FU in Caucasian patients as compared with Japanese patients. Comparison of the 5-FU pharmacokinetic parameters of S-1 suggests that the Caucasian population tends to demonstrate higher 5-FU concentrations with the same dose of S-1 as compared with Japanese patients. Further analyses indicate that the area under the curve (AUC) ratio of Tegafur/5-FU is higher when S-1 is administered to Japanese patients than when it is administered to Caucasian patients. It is speculated that Tegafur conversion – via CYP 2A6 – to 5-FU occurs faster in Caucasian patients than in Japanese patients (Shimada T, Yamazaki H, Guengerich FP. Ethnic-related differences in coumarin 7-hydroxylation activities catalyzed by cytochrome P4502A6 in liver microsomes of Japanese and Caucasian populations. *Xenobiotica*. 1996;26(4);359-403). These findings may be related to differences in the CYP 2A6 genetic polymorphism between Caucasian and Japanese patients.

Cisplatin is a heavy metal compound with cytotoxic activity. It inhibits DNA precursors, to a lesser extent it inhibits protein and RNA synthesis, and it causes intra-strand crosslinking of DNA, which is the primary mechanism of action. Because cisplatin cytotoxicity does not appear to be cell-cycle dependent, its toxicity is similar in all phases of the cell cycle. Several cytotoxic anti-cancer agents, including 5-FU, have been shown to be supra-additive or synergistic with cisplatin *in vitro* or *in vivo*. The basis for 5-FU interaction with cisplatin is unclear.

The present invention relates to a method for treating a diffuse-type or a mixed-type gastric cancer. It has been found that a combination therapy including both cisplatin and S-1 is effective in treating advanced gastric cancer, and that this combination therapy is particularly effective in treating gastric cancer classified as diffuse-type gastric cancer. An open-label, international, multicenter, two-arm, parallel, randomized Phase III study was conducted in which the efficacy and safety of a combination regimen of S-1 and cisplatin was compared to the efficacy and safety of a combination regimen of 5-FU and cisplatin in patients with advanced gastric cancer that was previously untreated with chemotherapy. Patients were stratified by the type of disease (e.g. locally advanced, 1 metastatic site, $\geq$ 2 metastatic sites), whether the patients had undergone prior adjuvant therapy, whether their disease was measurable versus non-measurable, and were randomized to receive one of two treatment regimens:

- S-1/cisplatin (CS): S-1, 25 mg/m² twice a day from Day 1 through Day 21, and cisplatin, 75 mg/m² on Day 1 of treatment, repeated every four weeks, with a maximum of 6 cycles of cisplatin.
- 5-FU/cisplatin (CF): 5-FU, 1000 mg/m²/24 hours on Days 1 through 5 and cisplatin, 100 mg/m² on Day 1, repeated every 4 weeks, with a maximum of 6 cycles of cisplatin.

The primary objective of this study was to compare the overall survival of S-1 + cisplatin therapy to 5-FU + cisplatin therapy in patients with advanced gastric cancer. The key secondary endpoints were overall response rate and progression-free survival analyzed for the full analysis set of the study population, as well as the safety and tolerability of the two chemotherapy regimens.

Several key findings were made from this study. First, although the difference in overall survival was not significant between the two population groups, the S-1/cisplatin combination demonstrated lower mortality risk than the 5-FU/cisplatin arm. Second, S-1 in combination with cisplatin demonstrated improved safety and tolerability in comparison to 5-FU/cisplatin: patients in the 5-FU/cisplatin arm were twice as likely to experience severe neutropenia as those in the S-1/cisplatin arm; patients in the 5-FU/cisplatin arm were nearly four times as likely to experience febrile neutropenia as patients in the S-1/cisplatin arm; patients in the 5-FU/cisplatin arm were 10 times more likely to experience stomatitis than those in the S-1/cisplatin arm; the overall incidence of renal-related adverse events was higher among patients in the 5-FU/cisplatin arm than among those in the S-1/cisplatin arm, and the mortality rate due to toxicity was cut in half in the S-1/cisplatin group compared to the 5-FU/cisplatin group. These results are compiled in Table 1.

Table 1

Adverse Event	S-1/cisplatin	5-FU/cisplatin
Grade $\geq$ 3 neutropenia	18.6%	40%
Grade $\geq$ 3 febrile neutropenia	1.7%	6.9%
Stomatitis	1.3%	13.6%
Renal related adverse events	18.8%	33.5%
Mortality rate due to toxicity	2.5%	4.9%

The data collected in this study was evaluated retrospectively for correlation of histological type of gastric cancer and overall survival. The analysis revealed that among

patients with diffuse-type gastric cancer, as well as a limited number of patients with mucinous-type gastric cancer, (292 patients in the S-1/cisplatin arm; 298 in the 5-FU/cisplatin arm), there was a significant difference in survival in favor of the S-1/cisplatin regimen. Overall survival for patients with advanced diffuse-type gastric cancer in the S-1/cisplatin arm was 9.0 months, whereas overall survival for patients in the 5-FU/cisplatin arm was 7.1 months. These findings are shown in Figure 1.

In addition, weight loss has been recognized as increasing the risk of death in cancer patients. It has been demonstrated that weight loss in patients receiving chemotherapy is associated with reduced survival. Patients with metastatic gastrointestinal cancers who present with weight loss receive less chemotherapy than patients without weight loss (Andreyev et al., Eur J Cancer 34(4), 503-9, 1998; DeWys et al. Am J Med. 69, 491-7, 1980; Ross PJ, Ashley S, when undergoing chemotherapy for lung cancers? Br J Cancer 2004;90, 1905-11). Recently, it was reported that, in addition to reduced dietary intake and mechanical obstruction by tumor, systemic inflammation may play an additional role in nutritional depletion (Deans DAC, Tan BH, Wigmore SJ, Ross JA, de Beaux AC, Paterson-Brown S, et al. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. Br J Cancer. 2009;100:63-69).

Based on these findings, it was investigated retrospectively in the above study whether weight loss prior to the beginning of treatment had an effect on the overall survival of patients. The analysis revealed that the overall survival in patients with no prior weight loss was significantly longer for patients in the S-1/cisplatin group than for those treated with 5-FU/cisplatin, with a median overall survival of 9.0 and 7.9 months in each group. Taking this factor into consideration as well as the factor that patients with metastatic diffuse-type gastric cancer fared better when treated with S-1/cisplatin, further analysis of the data revealed that patients with metastatic diffuse-type gastric cancer with <10% baseline weight loss treated with S-1/cisplatin had a significantly longer median overall survival (9.0 months) than similar patients treated with 5-FU/cisplatin (6.9 months). These results are shown in Figure 2.

Thus, in accordance with the present invention, a patient with a diffuse-type or mixed-type gastric cancer is treated by administering an effective amount of S-1 and an effective amount of cisplatin to the patient. The diffuse-type or mixed-type gastric cancer may be a diffuse-type or mixed-type gastric cancer at any stage of the disease. Specifically, the diffuse-type or mixed-type gastric cancer may be in an advanced stage. Generally, an advanced gastric

cancer is a stage II, III, or IV cancer. Further, the cancer which is to be treated by the invented method may have reached a metastatic disease state when the S-1/cisplatin combination is administered. Further, the method of the present invention may be used as a first-line, or as a neoadjuvant or adjuvant, therapy in the treatment of diffuse-type or mixed-type gastric cancers.

5 However, the method of the present invention may also be used as a second (or more)-line therapy to treat a patient who has previously received treatment for diffuse-type or mixed-type gastric cancer, including, but not limited to, tumor resection, radiation treatment, or prior chemotherapy.

In one aspect of the present invention, S-1 may be administered perorally. S-1
10 may be administered in an initial dose of about 20 mg/m² to about 80 mg/m² of Tegafur in S-1 per day. Preferably, S-1 may be given in an initial dose of about 30 mg/m² to about 80 mg/m² of Tegafur in S-1 per day. More preferably, S-1 may be given in an initial dose of about 50 mg/m² to about 70 mg/m² of Tegafur in S-1 per day. This dose may be administered in at least two
15 separate doses, such that S-1 is administered at least twice daily. In any administration of S-1, including initial amounts, S-1 may be given to the patient twice daily in two doses each of about 10 mg/m² to about 40 mg/m² of Tegafur in S-1, such that the total daily dose of S-1 is about 20 mg/m² to about 80 mg/m² of Tegafur in S-1. In a preferred embodiment, S-1 may be initially given to the patient twice daily in two doses each of about 15 mg/m² to about 40 mg/m² of
20 Tegafur in S-1, such that the total daily dose of S-1 is about 30 mg/m² to about 80 mg/m² of Tegafur in S-1. In a further preferred embodiment, S-1 may be initially given to the patient twice daily in two doses each of about 25 mg/m² to about 35 mg/m² of Tegafur in S-1, such that the total daily dose of S-1 is about 50 mg/m² to about 70 mg/m² of Tegafur in S-1. After the initial dose of S-1, the dose of S-1 may be adjusted downward in case the patient experiences any adverse effects due to the administration of S-1.

25 S-1 may be given in a dosing regimen which includes a dosing period and a rest period. In one embodiment of the present invention, S-1 is given to a patient at least twice daily for a period of about 7 to about 28 days, followed by a rest period of about 7 to about 14 days. Preferably, the dosing period and the rest period combined are not shorter than 28 days. Preferably, S-1 is administered at least twice daily for about 21 days. During the rest period, the
30 patient should not receive any doses of S-1. This results in the S-1 being administered for about 21 consecutive days within a period of about 28 to about 35 days. Further, some patients may respond better to a shorter rest period, whereas other patients may respond better to a longer rest

period. In treatment of patients of Japanese origin, for example, it has been found that a rest period of 14 days may be more appropriate. However, in patients of Caucasian origin, a 7-day rest period may be more appropriate.

In one embodiment of the invention, S-1 is administered at least one hour before or at least one hour after a meal. It has been found that the plasma concentrations of Oteracil potassium, one component of S-1, are significantly higher when S-1 is taken at least one hour before or at least one hour after a meal. Assuming that Oteracil potassium is important for protection of the gastro-intestinal tract, this suggests it may be optimal to administer S-1 under fasting conditions. For this reason, S-1 should not be taken within one hour of a meal.

In one aspect of the present invention, cisplatin may be administered intravenously. Cisplatin may be administered in conventional forms for intravenous administration as is well known to those in the art. In another embodiment of the present invention cisplatin is administered in an initial dose of about 50 mg/m² to about 100 mg/m². Preferably, cisplatin is administered in an initial dose of about 60 mg/m² to about 80 mg/m². In yet another embodiment of the present invention, cisplatin is administered in a single dose, followed by a rest period of about 28 to about 35 days. In particular, cisplatin may be administered in a dose of about 75 mg/m². During this rest period, the patient should receive no cisplatin. One may wish to provide a patient with a lower dose of cisplatin if the patient experiences adverse events related to the administration of cisplatin at the initial dose. A patient may receive multiple doses of cisplatin over the course of time, so long as there is a rest period between those doses.

Both cisplatin and S-1 should be administered to the patient within the same period of about 28 to about 35 days. However, it is not necessary to administer the dose of cisplatin at the same time as the first dose of S-1 is administered to the patient. Instead, the dose of cisplatin should be administered once within a period of about 28 to about 35 days, and the doses of S-1 should be administered 21 consecutive days within a period of about 28 to about 35 days.

It will be understood that reference to a weight of S-1 is a reference to the weight of Tegafur in the total mixture, rather than the weight of Gimeracil, Oteracil potassium, or of the total mixture. Furthermore, it will be understood that when a dose of S-1 or cisplatin is given in units of mg/m², the actual dose for a particular patient is to be determined by adjusting the weight of S-1 or cisplatin based on the patient's total body surface area.

S-1 may be administered in various peroral dosage forms, including (but not limited to) tablets, coated tablets, pills, powders, granules, capsules, solutions, suspensions, emulsions, etc. These may be prepared by conventional methods, using suitable pharmaceutically acceptable carriers. Examples of useful carriers are those widely used in the manufacture of conventional pharmaceutical compositions, such as fillers, extenders, binders, disintegrators, surfactants, lubricants and like diluents and excipients.

As the carrier for shaping into the form of tablets, there can be employed various excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, etc.; binders such as simple syrup, glucose solution, starch solution, gelatin solution, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate, polyvinylpyrrolidone, gum arabic powder, gum tragacanth powder, etc.; disintegrators such as dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene-sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride, starch, lactose, etc.; antidisintegrators such as sucrose, stearic acid, cacao butter, hydrogenated oil, etc.; absorption promoters such as quaternary ammonium bases, sodium lauryl sulfate, etc.; humectants such as glycerol, starch, etc.; adsorbents such as starch, lactose, kaolin, bentonite, colloidal silicic acid, etc.; and lubricants such as purified talc, stearic acid salts, boric acid powder, polyethylene glycol, etc. Where necessary, the tablets may be in the form of coated tablets such as sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, or double or multi-layer tablets, etc. Capsules are manufactured by mixing the antitumor composition with any of the carriers mentioned above and encapsulating the mixture in hard gelatin capsule, soft capsule or other capsules.

Cisplatin may be administered in intravenous dosage forms such as liquid. The preparation containing cisplatin may be prepared by conventional methods, using suitable pharmaceutically acceptable carriers. Examples of useful carriers are those widely used in the manufacture of conventional pharmaceutical compositions, such as diluents, and buffer agents. Cisplatin may be provided in a liquid form, that is administered intravenously as itself, or a solid form, that is prepared in a liquid form before use.

The present invention will be further illustrated by reference to the following examples, which are not intended to be limiting.

Example 1

1,053 patients with untreated, advanced gastric/gastroesophageal adenocarcinoma were randomized 1:1 to receive either S-1/cisplatin or 5-FU/cisplatin. Patients who received S-1/cisplatin were treated with 25 mg/m² of Tegafur in S-1, in the form of an oral capsule, twice daily (at least one hour before, or one hour after, a meal) on days 1 through 21 of the treatment cycle, followed by a 7 day rest period, as well as 75 mg/m² of cisplatin, in the form of continuous intravenous infusion, on day 1 of the treatment cycle, followed by a 28 day rest period. Patients who received 5-FU/cisplatin were treated with a 1000 mg/m² per day continuous intravenous infusion of 5-FU per day over a period of 5 days, followed by a 23 day rest period, as well as a 100 mg/m² continuous intravenous infusion of cisplatin on day 1, followed by a 28 day rest period.

Overall survival analyses for non-inferiority (NI), by pre-specified stratifications, and by the largest histologic subset (diffuse type histology) were performed. Overall survival for patients in the S-1/cisplatin group compared to patients in the 5-FU/cisplatin group had a hazard ratio (HR) of 0.92 (two-sided 95% CI, 0.80-1.05). HR was 1.05, being much lower than HR=1.22 derived from literature. Using a stringent HR non-inferiority margin (HR=1.10), S-1/cisplatin was found to be statistically significantly non-inferior to 5-FU/cisplatin (p=0.0068). The 74% preserved control effect by S-1/cisplatin was well above the suggested 50% by Rothmann et al. (Statist-Med 2003;22:239-264).

Out of 12 stratification subcategories, S-1/cisplatin produced overall survival HR≤ 1.0 in 9 and HR>=1.0 in 3. Overall survival analysis for diffuse-type or mixed-type histology (590 patients) showed that S-1/cisplatin (median survival of 9.0 months) resulted in superior overall survival (Log rank p<0.05; HR, 0.83 [95% CI, 0.70 to 0.99]) than 5-FU/cisplatin (median survival of 7.1 months). This analysis leads to the conclusion that patients with diffuse-type or mixed-type gastric cancer given the S-1/cisplatin treatment regimen had a statistically superior overall survival to those given the 5-FU/cisplatin treatment regimen.

Example 2

Patients with untreated, advanced diffuse-type or mixed-type gastric/gastroesophageal adenocarcinoma are randomized 2:1 to receive S-1/cisplatin or 5-FU/cisplatin, respectively. Patients with locally advanced disease and patients with more than 10% weight loss within 3 months prior to the study are excluded from the patient population.

Patients who receive S-1/cisplatin are treated with 25 mg/m² of Tegafur in S-1, in the form of an oral capsule, twice daily (at least one hour before, or one hour after, a meal) on days 1 through 21 of the treatment cycle, followed by a 7 day rest period, as well as with 75 mg/m² of cisplatin, in the form of continuous intravenous infusion, on day 1 of the treatment cycle, followed by a 28 day rest period. Patients who receive 5-FU/cisplatin are treated with a 1000 mg/m² per day continuous intravenous infusion of 5-FU per day over a period of 5 days, followed by a 23 day rest period, as well as with a 100 mg/m² continuous intravenous infusion of cisplatin on day 1, followed by a 28 day rest period.

Overall survival analyses for superiority are performed. Patients with diffuse-type or mixed-type gastric cancer given the S-1/cisplatin treatment regimen have a statistically superior overall survival to those given the 5-FU/cisplatin treatment regimen. It is concluded that S-1/cisplatin demonstrates superior overall survival to 5-FU/cisplatin in patients with diffuse-type or mixed-type of metastatic gastric cancer.

Example 3

Patients with untreated, advanced diffuse-type or mixed-type gastric/gastroesophageal adenocarcinoma are randomized 2:1 to receive S-1 or 5-FU, respectively. Patients with locally advanced disease and patients with more than 10% weight loss within 3 months prior to the study are excluded from the patient population. Patients who receive S-1 are treated with 25 mg/m² of Tegafur in S-1, in the form of an oral capsule, twice daily (at least one hour before, or one hour after, a meal) for a total daily amount of 50 mg/m² on days 1 through 21 of the treatment cycle, followed by a 7 day rest period. Patients who receive 5-FU are treated with a 1000 mg/m² per day continuous intravenous infusion of 5-FU per day over a period of 5 days, followed by a 23 day rest period.

Overall survival analyses for superiority are performed. Patients with diffuse-type or mixed-type gastric cancer given the S-1/cisplatin treatment regimen have a statistically superior overall survival to those given the 5-FU/cisplatin treatment regimen. S-1 is also found to have lower mortality risk than 5-FU. In addition, S-1 shows a favorable safety and tolerability to 5-FU. It is concluded that S-1 demonstrates superior overall survival to 5-FU in patients with diffuse-type or mixed-type of metastatic gastric cancer.

The above examples suggest that S-1, administered with or without cisplatin, should be effective in treating diffuse-type gastric cancers and mixed-type gastric cancers, along

with treating other diffuse-type cancers in general. Other cancers that present with a diffuse-type histology include the following: colorectal cancer, bladder cancer, pancreatic cancer, biliary cancer, appendix cancer, esophageal cancer, non-small cell lung cancer (NSCLC), and breast cancer. In order to treat these types of cancers, S-1 can be administered to a patient at least twice daily in a total daily amount of about 20 mg/m² to about 80 mg/m² of Tegafur in S-1. Preferably, the total daily amount of S-1 initially administered to the patient is about 30 mg/m² to about 80 mg/m² of Tegafur in S-1, subject to possible reduction in the event of unwanted side effects. More preferably, S-1 may be administered to a patient at least twice daily in a total daily amount of 50 mg/m² to 70 mg/m² of Tegafur in S-1. S-1 may be provided in peroral formulations as described above for the treatment of diffuse-type gastric cancer or mixed-type gastric cancer. In some patients, S-1 may be administered to the patient at least twice daily for a period of about 7 to about 28 days, followed by a rest period of about 7 to about 14 days. Japanese patients generally respond better to a dosing regimen that including administering S-1 at least twice daily for a period of about 28 days followed by a rest period of about 14 days, such that S-1 is administered over about 28 consecutive days in a 42 day period. Other, non-Japanese patients may respond better to a dosing regimen that includes administering S-1 at least twice daily for a period of about 14 days followed by a rest period of about 7 days, such that S-1 is administered over about 14 consecutive days in a 21 day period. S-1 may be provided in peroral formulations as described above for the treatment of diffuse-type gastric cancer or mixed-type gastric cancer.

The publications and other materials cited herein to illuminate the background of the invention and to provide additional details respecting the practice of the invention are incorporated herein by reference to the same extent as if they were individually indicated to be incorporated by reference. In addition, the following publications may be useful in understanding the invention, and are also hereby incorporated by reference:

1. Mayer RJ. Gastrointestinal tract cancer. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson, JL, Isselbacher KJ, eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York, NY:McGraw Hill, 2005.
2. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20.

3. Murad AM, Santiago FF, Petroianu A, et al. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993;72:37-41.
4. Pyrhönen S, Kuitunen T, Nyandoto P, et al. Randomised comparison of
5 fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care
with supportive care alone in patients with metastatic gastric cancer. *Br J
Cancer* 1995;71:587-91.
5. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C,
et al. Phase III study of docetaxel and cisplatin plus fluorouracil as first-line
10 therapy for advanced gastric cancer: a report of the V325 study group. *J Clin
Oncol* 2006;24:4991-7.
6. Kang Y, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Randomized
phase III trial of capecitabine/cisplatin (XP) vs. continuous infusion of 5-
FU/cisplatin (FP) as first-line therapy in patients with advanced gastric cancer
15 (AGC). *J Clin Oncol* 2006;24:17S (abstr LBA4018).
7. Park JM, Jang YJ, Kim JH, Park SS, Park, SH, Kim SJ, et al. Gastric cancer
histology: Clinicopathologic characteristics and prognostic value. *J Surg Oncol.*
2008;98:520–25.
8. Lee KH, Lee JH, Cho JK et al. A prospective correlation of Lauren's
20 histological classification of stomach cancer with clinicopathological findings
including DNA flow cytometry. *Pathology Research and Practice.* 2001;197
(4):223–9.
9. Patel PR, Yao JC, Hess K, Schnirer I, Rashid A, Ajani JA. Effect of timing of
metastasis/disease recurrence and histological differentiation on survival of
25 patients with advanced gastric cancer. *Cancer.* 2007;110:2186–90.
10. Ichikawa et al., *Intern. J Cancer* 112, 967–73, 2004
11. Andreyev et al., *Eur J Cancer* 34(4), 503–9, 1998
12. DeWys et al. *Am J. Med.* 69, 491-7, 1980
13. Ross PJ, Ashley S, Norton A, Priest K, Waters JS, Eisen T, et al. Do patients
30 with weight loss have a worse outcome when undergoing chemotherapy for
lung cancers? *Br. J Cancer* 2004;90,1905–11.

14. Deans DAC, Tan BH, Wigmore SJ, Ross JA, de Beaux AC, Paterson-Brown S, et al. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. *Br J Cancer*. 2009;100:63–69.
- 5 15. Takechi T, Nakano K, Uchida J, et al. Antitumor activity and low intestinal toxicity of S-1, a new formulation of oral tegafur, in experimental tumor models in rats. *Cancer Chemother Pharmacol*. 1997;39(3):205-211.
16. Fukushima M, Shimamoto Y, Kato T, et al. Anticancer activity and toxicity of S-1, an oral combination of tegafur and two biochemical modulators, compared with continuous i.v. infusion of 5-fluorouracil. *Anti-Cancer Drugs*. 1998;9:817-823.
- 10 17. Fukushima M, Sataka H, Uchida J, et al. Preclinical antitumor efficacy of S-1: a new oral formulation of 5-fluorouracil on human tumor xenografts. *International J Oncology*. 1998;13:693- 698.
- 15 18. Koizumi W, Kurihara M, Nakano S, et al. Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. *Oncology*. 2000;58:191-197.
19. Ohtsu A, Baba H, Sakata Y, et al and the S-1 Cooperative Colorectal Carcinoma Study Group. Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. *Br J Cancer*. 2000;83(2):141-145.
- 20 20. Cohen SJ, Leichman CG, Yeslow G, et al. Phase I and pharmacokinetic study of once daily oral administration of S-1 in patients with advanced cancer. *Clin Cancer Res*. 2002;8:2116–2122.
- 25 21. Phase I study to determine the safety and pharmacokinetics of oral administration of BMS-247616 on a once daily schedule for twenty-eight days with seven days rest in patients with solid tumors. Bristol-Myers Squibb Company Clinical Study Report (CA 157004). 2003.
22. Ajani J, Yao J, Faust J, et al. Phase I pharmacokinetic study of S-1 plus cisplatin in patients with advanced gastric carcinoma (AGC). *ASCO*. 2004;Abstract 4043.
- 30

23. Yver AJ, Ajani J, Moiseyenko VM, et al. Final results of a randomized controlled phase III trial (TAX 325) comparing docetaxel (T) combined with cisplatin (C) and 5-fluorouracil (F) to CF in patients (pts) with metastatic gastric adenocarcinoma (MGC). ASCO. 2005;Abstract 4002.
- 5 24. Comets E, Ikeda K, Hoff P, Fumoleau P, Wanders J, Tanigawara Y. Comparison of the pharmacokinetics of S-1, an oral anticancer agent, in Western and Japanese patients. J Pharmacokinetics and Pharmacodynamics 2003;30(4):257-283.
- 10 25. Ohtsu, A, Shimada Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol. 2003;21:54-59.
- 15 26. Lenz H, Lee FC, Haller DG, et al. Extended safety and efficacy data on S-1 plus cisplatin in patients with advanced gastric carcinoma in a multicenter phase II study. J Clin Oncol. 2006; ASCO Annual Meeting Proceedings Part 1. Vol 24, No. 18S.Abstract 4083.

20 While the invention has been disclosed by reference to the details of preferred embodiments of the invention, it is to be understood that the disclosure is intended in an illustrative rather than a limiting sense, as it is contemplated that modifications will readily occur to those skilled in the art, within the spirit of the invention.

Claims

- [Claim 1] A method for treating a diffuse-type gastric cancer or a mixed-type gastric cancer in a patient in need of such treatment which comprises (i) administering to the patient an effective amount of S-1, wherein said S-1 is a pharmaceutical composition containing Tegafur, Gimeracil, and Oteracil potassium at a molar ratio of 1:0.4:1, and (ii) administering to the patient an effective amount of cisplatin.
- [Claim 2] The method of claim 1, wherein said S-1 is administered at least twice daily in a total daily amount of about 20 mg/m² to about 80 mg/m² of Tegafur in S-1.
- 10 [Claim 3] The method of claim 2, wherein the total daily amount of Tegafur in S-1 is initially about 30 mg/m² to about 80 mg/m².
- [Claim 4] The method of claim 3, wherein the total daily amount of Tegafur in S-1 is initially about 50 mg/m² to about 70 mg/m².
- [Claim 5] The method of claim 1, wherein said S-1 is administered for about 7 to about 28 consecutive days within a period of about 14 to about 35 days.
- 15 [Claim 6] The method of claim 3, wherein said S-1 is administered for about 21 consecutive days within a period of about 28 days.
- [Claim 7] The method of claim 4, wherein said patient is a Caucasian patient.
- [Claim 8] The method of claim 5, wherein said effective amount of cisplatin comprises about 75 mg/m² of cisplatin and said cisplatin is administered once in a period of about 28 days.
- 20 [Claim 9] The method of claim 1, wherein said S-1 is administered at least one hour before or after a meal.
- [Claim 10] The method of claim 1, wherein said S-1 is administered perorally.
- 25 [Claim 11] The method of claim 1, wherein said cisplatin is administered intravenously.
- [Claim 12] The method of claim 1, wherein said cisplatin is administered once in a period of about 28 to about 35 days.

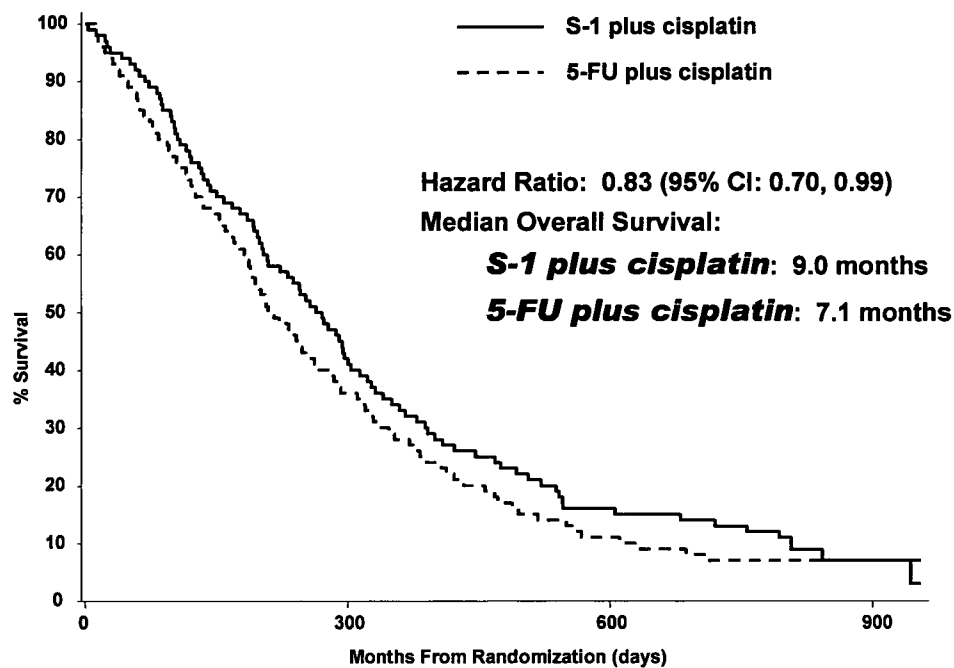
- [Claim 13] The method of claim 10, wherein said cisplatin is administered once in a period of about 28 days.
- [Claim 14] The method of claim 10, wherein said S-1 is administered for about 7 to about 28 consecutive days within a period of about 14 to about 35 days, and wherein said
5 cisplatin is administered once on the first day or once on the eighth day on which S-1 is administered.
- [Claim 15] The method of claim 1, wherein said cisplatin comprises about 50 mg/m² to about 100 mg/m² of cisplatin.
- [Claim 16] The method of claim 13, wherein said cisplatin comprises about 60 mg/m² to
10 about 80 mg/m² of cisplatin.
- [Claim 17] The method of claim 1, wherein said diffuse-type gastric cancer or mixed-type gastric cancer is an advanced diffuse-type gastric cancer or advanced mixed-type gastric cancer.
- [Claim 18] The method of claim 15, wherein said advanced diffuse-type gastric cancer or
15 advanced mixed-type gastric cancer is metastatic diffuse-type gastric cancer or metastatic mixed-type gastric cancer.
- [Claim 19] The method of claim 15, wherein said advanced diffuse-type gastric cancer or advanced mixed-type gastric cancer has not been previously treated with chemotherapy.
- [Claim 20] The method of claim 1, wherein said patient has not lost more than 10% of his or
20 her baseline weight.
- [Claim 21] A method for treating an advanced diffuse-type gastric cancer in a patient in need of such treatment which comprises (i) perorally administering to the patient S-1 in an amount of about 10 mg/m² to about 40 mg/m² of Tegafur in the S-1
25 twice daily at least one hour before or after a meal for about 7 to about 28 consecutive days within a period of about 14 to about 35 days, wherein said S-1 is a pharmaceutical composition containing Tegafur, Gimeracil, and Oteracil potassium at a molar ratio of 1:0.4:1, and (ii) intravenously administering to the patient about 50 mg/m² to about 100 mg/m² of cisplatin once in a period of about
30 28 to about 35 days.

- [Claim 22] The method of claim 21, wherein the S-1 is in an initial amount of about 15 mg/m² to about 40 mg/m² of Tegafur in the S-1.
- [Claim 23] Use of a combination of first preparation consisting of therapeutically effective amount of S-1, wherein said S-1 is a pharmaceutical composition containing
5 Tegafur, Gimeracil, and Oteracil potassium at a molar ration of 1:0.4:1, and second preparation containing therapeutically effective amount of cisplatin for preparation of medicament for the treatment of a diffuse-type gastric cancer or a mixed gastric cancer.
- [Claim 24] The use of claim 23 wherein a total daily amount of Tegafur in S-1 is about 20
10 mg/m² to about 80 mg/m².
- [Claim 25] The use of claim 23 wherein S-1 is administered for about 7 to about 28 consecutive days within the period of about 14 days to about 35 days.
- [Claim 26] The use of claim 23 wherein said cisplatin is administered once in a period of about 28 days.
- 15 [Claim 27] The use of claims 23 wherein the therapeutically effective amount of cisplatin is about 50 mg/m² to about 100 mg/m².
- [Claim 28] The use of claim 23, wherein the therapeutically effective amount of cisplatin is about 60 mg/m² to about 80 mg/m².
- [Claim 29] A kit for the treatment of a diffuse-type gastric cancer or a mixed gastric cancer,
20 comprising a first preparation consisting of therapeutically effective amount of S-1, wherein said S-1 is a pharmaceutical composition containing Tegafur, Gimeracil, and Oteracil potassium at a molar ration of 1:0.4:1, and a second preparation containing therapeutically effective amount of cisplatin.
- [Claim 30] The kit of claim 29, wherein a total daily amount of Tegafur in S-1 is about 20
25 mg/m² to about 80 mg/m².
- [Claim 31] The kit of claim 29, wherein S-1 is administered for about 7 to about 28 consecutive days within the period of about 14 days to about 35 days.
- [Claim 32] The kit of claim 29, wherein said cisplatin is administered once in a period of about 28 days.

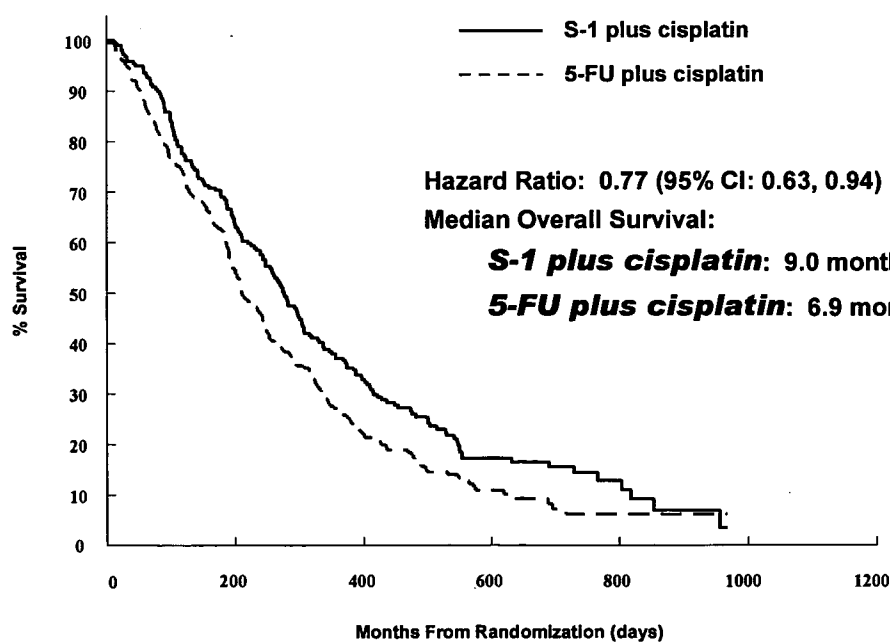
- [Claim 33] The kit of claim 29, wherein the therapeutically effective amount of cisplatin is about 50 mg/m² to about 100 mg/m².
- [Claim 34] The kit of claim 29, wherein the therapeutically effective amount of cisplatin is about 60 mg/m² to about 80 mg/m².
- 5 [Claim 35] A combination of first preparation consisting of therapeutically effective amount of S-1, wherein said S-1 is a pharmaceutical composition containing Tegafur, Gimeracil, and Oteracil potassium at a molar ration of 1:0.4:1, and second preparation containing therapeutically effective amount of cisplatin for the treatment of a diffuse-type gastric cancer or a mixed gastric cancer.
- 10 [Claim 36] The combination of claim 35, wherein a total daily amount of Tegafur in S-1 is about 20 mg/m² to about 80 mg/m².
- [Claim 37] The combination of claim 35, wherein S-1 is administered for about 7 to about 28 consecutive days within the period of about 14 days to about 35 days.
- [Claim 38] The combination of claim 35, wherein said cisplatin is administered once in a
15 period of about 28 days.
- [Claim 39] The combination of claim 35, wherein the therapeutically effective amount of cisplatin is about 50 mg/m² to about 100 mg/m².
- [Claim 40] The combination of claim 35, wherein the therapeutically effective amount of cisplatin is about 60 mg/m² to about 80 mg/m².

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[Fig. 1]



[Fig. 2]



INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2010/058400

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. A61K33/24 (2006.01) i, A61K31/44 (2006.01) i, A61K31/513 (2006.01) i,
A61K31/53 (2006.01) i, A61P1/00 (2006.01) i, A61P35/00 (2006.01) i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. A61K33/24, A61K31/44, A61K31/513, A61K31/53, A61P1/00, A61P35/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996
Published unexamined utility model applications of Japan 1971-2010
Registered utility model specifications of Japan 1996-2010
Published registered utility model applications of Japan 1994-2010

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS/MEDLINE/EMBASE/BIOSIS (STN), JSTPlus/JMEDPlus/JST7580 (JDreamII)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	W. KOIZUMI et al, Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer, British Journal of Cancer, 2003, Vol.89, p.2207-2212	23-40
A	JP 2007-534634 A (TAIHO PHARMACEUTICAL CO., LTD.) 2007.11.29, Claims 11-13 and 29-30, [0037] & US 2008/0166427 A1 & EP 1750703 A & WO 2005/105086 A1	23-40
A	T. KONDO et al, Antitumor Effect of S-1 and Cisplatin Treatment against Human Gastric Cancer Xenografted in Nude Mice, Gan to Kagaku Ryoho, 1997, Vol.24, No.9, p.1103-1108	23-40



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

14.06.2010

Date of mailing of the international search report

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Name and mailing address of the ISA/JP

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3336

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2010/058400

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	H. WATAYA et al, A new antitumor drug: S-1, Gekkan Kokyukika, 2005, Vol.7, NO.5, p.496-501	23-40
A	K. TSUTSUMI et al, Saihatsu shinko igan ni taisuru S1 wo chushin to shita kagakuryouhou no kentou (Investigation of S1-based chemotherapy against recurrent or advanced gastric cancer), Journal of Japan Surgical Society, 2003, Vol.104, Special Edition, p.638	23-40
A	Emmanuelle COMETS et al, Comparison of the Pharmacokinetics of S-1, an Oral Anticancer Agent, in Western and Japanese Patients, Journal of Pharmacokinetics and Pharmacodynamics, 2003, Vol.30, No.4, p.257-283	23-40

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2010/058400

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-22
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claims 1-22 relates to a method for treatment of the human body by surgery or therapy, which does not require an intentional search by the International Searching Authority in accordance with PCT Article 17(2)(a)(i) and [Rule 39.1(iv)].
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.