PERGAMON

European Journal of Cancer 39 (2003) 1264–1270

European Journal of Cancer

www.ejconline.com

# Phase II trial with S-1 in chemotherapy-naïve patients with gastric cancer. A trial performed by the EORTC Early Clinical Studies Group (ECSG)

P. Chollet[a,*], P. Schöffski[b], K. Weigang-Köhler[c], J.H.M. Schellens[d], H. Cure[a], N. Pavlidis[e], V. Grünwald[b], R. De Boer[f], J. Wanders[f], P. Fumoleau[g]

[a]*Department of Medical Oncology, Centre Jean-Perrin, 58 Rue Montalembert, F-63011 Clermont-Ferrand, Cedex 1, France*
[b]*Abteilung Hämatologie und Onkologie, Medizinische Hochschule Hannover, Carl-Neuberg Str. 1, Hannover D-30625, Germany*
[c]*Klinikum Nürnberg, Prof.-Ernst-Nathan-Str. 1, 90419 Nürnberg, Germany*
[d]*Antoni van Leeuwenhoek Ziekenhuis/The Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam 1066 CX, The Netherlands*
[e]*Department Medical Oncology, University of Ioannina, Panepistimiou 1, 45500 Ioannina, Greece*
[f]*NDDO Oncology, Noordhollandstraat 71, Amsterdam 1081 AS, The Netherlands*
[g]*Department of Medical Oncology, Centre René Gauducheau, Site Hospitalier Nord, Bd Jacques Monod, Saint-Herblain F-44805, France*

Received 3 February 2003; accepted 14 February 2003

**Abstract**

S-1 is a new oral fluorinated pyrimidine derivate, in which the oral 5-fluorouracil (5-FU) prodrug, tegafur, was combined with two 5-FU-modulating substances, 5-chloro-2,4-dihydroxypyridine (gimeracil), and potassium oxonate (oteracil), at a molar ratio of 1:0.4:1. The final mechanism of action is exerted by 5-FU. The present study is the first European phase II trial of S-1 in gastric cancer. The primary study objectives were the safety, toxicity and activity of S-1 in non-pretreated patients with gastric cancer. The secondary objective was the duration of response. Patients had to have histologically- or cytologically-verified metastatic or locally advanced, unresectable gastric cancer; S-1 was administered orally twice daily at 40, then 35 mg/m$^2$ for 28 days every 5 weeks. The starting dose of 40 mg/m$^2$ was found to be intolerable due to significant non-haematological toxicity, and this dose was rapidly reduced to 35 mg/m$^2$ twice daily. Of the 7 patients enrolled at the 40 mg/m$^2$ level, only 3 were evaluable. At 35 mg/m$^2$, a response rate of 26.1% (95% Confidence Interval (CI) 12.0–45.1%) in 23 enrolled patients, and 31.6% (C.I. 14.7–53.0%) in 19 evaluable patients according to an independent radiology review, was found. The median duration of response at 35 mg/m$^2$ (6 patients) was 223 days (range, 108–828 days), and of stable disease was 111 days (range 68–411 days). S-1 can be administered with an acceptable safety and toxicity in European patients at a dose of 35 mg/m$^2$ days 1 – 28 every 5 weeks and is associated with a moderate response rate similar to the results achieved with other fluoropyrimidines.


*Keywords:* Gastric cancer; Adenocarcinoma; Oral fluoropyrimidines; Tegafur; Gimeracil; Oteracil; Palliative chemotherapy

## 1. Introduction

The incidence of stomach cancer has gradually decreased over recent decades; however, it remains the second leading cause of cancer-related death in the world after lung cancer. In the United States, this tumour type is now only the 14th cause of cancer mortality. However, this improvement is due to a decrease in incidence, and not to a favourable change in the curability rates [1].

In spite of substantial surgical efforts, results after resection of this tumour are dismal [1–4], and most patients develop recurrent or metastatic disease. Only a small number of chemotherapeutic agents provide active palliation in this disease, including fluoropyrimidines, anthracyclines and platinum compounds [1–5]. Single agent trials have shown that the objective response rates to drugs such as 5-fluorouracil (5-FU), mitomycin C, etoposide or cisplatin (CDDP) are usually less than 20%. Furthermore, the

* Corresponding author. Tel.: +33-4-7327-8005; fax: +33-4-7327-8029.
*E-mail address:* recherche.clinique@cjp.u-clermont1.fr (P. Chollet).

0959-8049/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0959-8049(03)00237-5

achieved responses are mainly partial and of short duration.

Combination trials have not resulted in improved survival compared with single-agent treatment. In addition, several randomised phase III studies have failed to define a gold standard combination regimen for the palliation of gastric cancer. Most commonly, combinations of CDDP and 5-FU, with or without anthracyclines, are used for this purpose but, at present, there is no consensus regarding standard chemotherapy for patients with advanced gastric carcinoma.

A review of single-agent activity in more recent phase II clinical trials in advanced gastric cancer has without exception shown disappointing results [5]. Clearly, novel drugs and combinations are needed to improve the efficacy of treatment.

More recent chemotherapy combinations for the treatment of gastric cancer involve prolonged or continuous infusion of 5-FU, and the use of modulating agents such as folinic acid to potentiate the limited activity of the fluoropyrimidine. Oral administration of 5-FU is not effective, due to the inability to achieve plasma concentrations of sufficient magnitude and due to variable pharmacokinetics.

An interesting way to increase the efficacy of 5-FU is through the inhibition of the degrading enzyme, dihydropyrimidine dehydrogenase (DPD).

S-1 is a new oral fluorinated pyrimidine derivative, in which tegafur has been combined with two 5-FU-modulating substances, 5-chloro-2,4-dihydroxypyridine (gimeracil), and potassium oxonate (oteracil), at a molar ratio of tegafur:gimeracil:oteracil = 1:0.4:1 [6].

Tegafur is an older prodrug of 5-FU, which is well absorbed after oral ingestion [7] and gradually converted to 5-FU in the liver.

Gimeracil inhibits the degradation of 5-FU by inhibition of DPD; at this level, it is approximately 200-fold more active than uracil [8]. When combined with 5-FU, this results in the prolonged maintenance of 5-FU concentrations, both in plasma and in tumours.

Oteracil is an agent that decreases the phosphorylation of 5-FU in the gastrointestinal tract by inhibiting the enzyme pyrimidine phosphoribosyl transferase, i.e. orally reducing the gastrointestinal toxicity without compromising the systemic efficacy of the fluoropyrimidine [9].

However, the final mechanism of action of S-1 is exerted by 5-FU.

S-1 has undergone phase I evaluation in Japan [10], as well as extensive phase II studies in gastric, colon, head and neck and breast cancers [11–16] leading to registration in this country for gastric cancer (TS-1®). It is now used in Japan in combination trials, and a number of Phase III studies involving S-1 are already underway. More recently, the drug was tested in phase I/II trials in Western countries [17].

The present article describes the results of the first European phase II trial of S-1 in patients with gastric cancer, a study performed by the Early Clinical Studies Group (ECSG) of the EORTC.

## 2. Patients and methods

The main objectives of this trial were to assess the response rate to S-1 in non-pretreated gastric cancer patients with locally advanced and/or metastatic disease; and to evaluate the tolerance and toxicity of this oral compound in European patients. The secondary objective was the duration of response. The trial was designed [18] as a multicentre non-randomised, single-agent phase II study and was performed in nine sites.

Patient selection criteria included histologically- or cytologically-verified metastatic or locally advanced, unresectable gastric cancer with at least one bidimensionally measurable lesion (verified by cytology or pathology if a single lesion); World Health Organization (WHO) performance status $<=2$; life expectancy $>3$ months; a minimal blood cell count of 2000 neutrophils and 100 000 platelets per μl with minimal haemoglobin 90 g/l; serum creatinine $<140$ μmol/l, with creatinine clearance $>1$ ml/s, if the serum creatinine was between 100 and 140 μmol/l; no prior chemotherapy for advanced disease; no radiotherapy for 4 weeks; no pre-irradiated target lesion, except if proven progression; no concomitant allopurinol or phenytoin. Written informed consent was obtained from all participating patients.

Based on the results of a previous phase I study performed by the ECSG [17], a schedule of S-1 administered twice daily for 28 consecutive days every 5 weeks at a dose of 35 mg/m$^2$ was recommended for heavily pretreated patients, and 40 mg/m$^2$ for minimally or non-pretreated patients. For this reason, the dose of 40 mg/m$^2$ twice daily was chosen for this trial in non-pretreated patients with gastric cancer, that was already known to be active in Japanese cancer patients. S-1 was administered between 7–10 am and 7–10 pm, within 1 h after a meal; treatment was replaced in cases of vomiting intact capsules. Patients were instructed to complete diary cards, noting drug intake and tolerance problems.

After a protocol amendment, the initial dose had to be decreased from 40 to 35 mg/m$^2$ twice daily due to toxicity observed in this and another phase II trial of the ECSG in patients with gastrointestinal malignancies.

The response evaluation by the investigators was confirmed by an independent radiology review. The progression and duration of response dates were determined by the independent radiologist, except when not possible (e.g. clinically assessable lesions); in that case, the investigators' assessments were used.

The response rate was determined on the evaluable patients and also on the 'intent-to-treat' population.

Patient compliance for this oral treatment was checked with the patient diary card and with a comparison of dispensed and returned capsules from the patient at each course

All case report forms were monitored, and full source data verification was performed against source documents on each site by NDDO Oncology, Amsterdam.

## 3. Results

### 3.1. Eligibility and evaluability

Table 1 summarises the characteristics of the enrolled patients. Among a total of 30 patients, 28 patients were found to be eligible according to the patient selection criteria of the protocol. 2 patients in the 40 mg/m$^2$ cohort were ineligible due to no measurable lesions at baseline. 22 patients were evaluable for response; all patients were evaluable for safety and tolerance.

4 out of 7 patients in the 40 mg/m$^2$ cohort were found not to be evaluable (2 without measurable lesions at baseline, 1 without measurable lesion at course 2, 1 went off the study for toxicity prior to evaluation). Among 23 patients treated at 35 mg/m$^2$, 4 were found to be inevaluable, 3 for insufficient duration of treatment (only 6, 16 and 19 days, respectively), and 1 for absence of tumour evaluation.

### 3.2. Efficacy

Among 3 evaluable patients in the 40 mg/m$^2$ dose group, the best response was stable disease in 1 patient. Among 19 evaluable patients in the 35 mg/m$^2$ cohort, 5 patients achieved a partial response and 1 patient a complete response, as confirmed by an independent review.

Table 1
Patients' characteristics

| Variable | Treatment group | |
|---|---|---|
| | 40 mg/m$^2$ (7 patients) | 35 mg/m$^2$ (23 patients) |
| Age (years) Median (range) | 57 (45–71) | 66 (38–79) |
| Gender | | |
| Female (*n*) | 4 | 6 |
| Male (*n*) | 3 | 17 |
| Performance status (WHO grade) | | |
| 0 (*n*) | 3 | 8 |
| 1 (*n*) | 2 | 12 |
| 2 (*n*) | 1 | 3 |
| Not known (*n*) | 1 | 0 |
| Prior treatment | | |
| Prior gastrectomy | 4 | 11 |

WHO, World Health Organization.

This results in a response rate of 26.1% (95% confidence interval (CI) 12.0–45.1%) among the 23 enrolled patients, or 31.6% (C.I. 14.7–53.0%) among the 19 evaluable patients.

The responses were seen mainly in the liver, lung and lymph nodes with improvement in ascites in a number of patients.

In the evaluable patients treated in the 35 mg/m$^2$ cohort, the median time to progression was 140 days (range 33–828+ days), the median duration of response was 223 days (range, 108–828+days), and the median duration of stable disease 111 days (range 68–411 days).

### 3.3. Safety

Safety was assessed for all treated patients. Non-haematological adverse events already present at baseline were reported only if they worsened in grade after treatment.

At the 40 mg/m$^2$ starting dose, 6/7 patients continued for a second course, of which 1 had a dose reduction. In total, 38 courses have been given to 7 patients; 1 patient received up to 18 courses.

At the 35 mg/m$^2$ starting dose, 18/23 patients continued for a second course, of which 6 had a dose reduction. In total, 78 courses were given to 23 patients; 1 patient received up to 18 courses. The median number of cycles in this cohort was 3, with a range of 1–18.

*Non-haematological adverse events* were mainly fatigue diarrhoea, nausea, vomiting, skin toxicities and increased serum bilirubin. They are summarised in Table 2. Diarrhoea was found to be the most relevant side-effect. At the 40 mg/m$^2$ starting dose, grade 4 diarrhoea was reported in one course in 1 patient, grade 3 in two courses in 1 patient, grade 2 in one course in 1 patient and grade 1 in four courses in 2 patients. Overall, diarrhoea was thus observed in 8/38 courses (21%), with grade 3 and 4 diarrhoea in 8% of courses.

At the 35 mg/m$^2$ starting dose, none out of 23 patients had a grade 4 diarrhoea, grade 3 was observed in three courses in 3 patients, grade 2 in three courses in 3 patients and grade 1 in 16 courses in 5 patients. Overall, diarrhoea was observed in 22/78 courses (28%), but grade 3 and 4 diarrhoea was seen in only 4% of courses.

Hand–foot syndrome (HFS) occured in 3 patients (35 mg/m$^2$ starting dose). 2 patients had grade 1 and 13 patient grade 3 HFS, developing from grade 1 to grade 3 during courses 4–12. One out of 7 patients at the 40 mg/m$^2$ starting dose experienced grade 2 hyperbilirubinaemia. Similarly, 3 out of 23 patients at the 35 mg/m$^2$ starting dose had hyperbilirubinaemia, possibly related to treatment.

*Haematological adverse events* were mainly anaemia, leucopenia, neutropenia and thrombocytopenia. These

Table 2
Non-haematological adverse events, worst grade per course per patient (possibly, probably or definitely related)

| | | Starting dose level 40 mg/m$^2$ | | | | | Starting dose level 35 mg/m$^2$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | CTC grade (38 courses) | | | | No. pts $N=7$ | CTC grade (78 courses) | | | | No. pts $N=23$ |
| Body group | Adverse event | 1 | 2 | 3 | 4 | Total | 1 | 2 | 3 | 4 | Total |
| Body as a whole—general disorders | Asthenia | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 2 |
| | Back pain | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Fatigue | 3 | 14 | 3 | 0 | 4 | 12 | 9 | 0 | 0 | 10 |
| | Fever | 1 | 2 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| | Malaise | 5 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Oedema peripheral | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| | Syncope | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Cardiovascular disorders, general | Hypertension | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Hypotension | 0 | 0 | 1 | 0 | 1 | 2 | 0 | 0 | 0 | 1 |
| Central and peripheral nervous system disorders | Dizziness | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 2 |
| | Dysaesthesia | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| | Vertigo | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 1 | 0 | 2 |
| Gastrointestinal system disorders | Abdominal pain | 2 | 1 | 0 | 0 | 1 | 1 | 3 | 0 | 0 | 2 |
| | Constipation | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| | Diarrhoea | 4 | 1 | 2 | 1 | 5 | 16 | 3 | 3 | 0 | 11 |
| | Flatulence | 0 | 0 | 0 | 0 | 0 | 5 | 2 | 0 | 0 | 3 |
| | Gastritis | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Hypersalivation | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Mouth dry | 0 | 0 | 0 | 0 | 0 | 12 | 0 | 0 | 0 | 5 |
| | Nausea | 5 | 1 | 0 | 0 | 4 | 8 | 3 | 0 | 0 | 10 |
| | Stomatitis | 2 | 0 | 0 | 0 | 2 | 18 | 2 | 0 | 0 | 7 |
| | Vomiting | 2 | 4 | 2 | 0 | 5 | 5 | 1 | 0 | 0 | 5 |
| Heart rate and rhythm disorders | Palpitation | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Liver and biliary system disorders | Bilirubin increased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Metabolic and nutritional disorders | Dehydration | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 |
| | Weight decrease | 6 | 0 | 0 | 0 | 3 | 3 | 1 | 0 | 0 | 2 |
| | Xerophthalmia | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Platelet, bleeding and clotting disorders | Coagulation disorder | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| | Epistaxis | 0 | 0 | 0 | 0 | 0 | 16 | 1 | 1 | 0 | 6 |
| | Haematoma | 4 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Petechiae | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Psychiatric disorders | Anorexia | 5 | 0 | 0 | 0 | 1 | 6 | 2 | 0 | 0 | 3 |
| | Appetite lost | 0 | 0 | 0 | 0 | 0 | 4 | 3 | 0 | 0 | 2 |
| | Sleepiness | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Reproductive disorders, male | Posthitis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Resistance mechanism disorders | Healing impaired | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| | Infection | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Sepsis | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Respiratory system disorders | Dyspnoea | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| | Rhinitis | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 1 |
| | Rhinorrhoea | 4 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Skin and appendages disorders | Alopecia | 7 | 0 | 0 | 0 | 1 | 4 | 0 | 0 | 0 | 1 |
| | Blisters | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| | Eruption | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| | Erythema | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Hyperpigmentation | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 |
| | Skin nail changes | 3 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 |
| | Pigmentation abnormal | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 3 |
| | Pruritus | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |

(*continued on next page*)

Table 2 (*continued*)

| Body group | Adverse event | Starting dose level 40 mg/m$^2$ CTC grade (38 courses) 1 | 2 | 3 | 4 | No. pts $N=7$ Total | Starting dose level 35 mg/m$^2$ CTC grade (78 courses) 1 | 2 | 3 | 4 | No. pts $N=23$ Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rash | 3 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Hand–foot syndrome | 0 | 0 | 0 | 0 | 0 | 7 | 9 | 3 | 0 | 3 |
| | Skin dry | 2 | 0 | 0 | 0 | 1 | 11 | 0 | 0 | 0 | 4 |
| | Sweating increased | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Special senses, other disorders | Taste alteration | 4 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Taste loss | 1 | 2 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Urinary system disorders | Dysuria | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Vascular (extracardiac) disorders | Flushing | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 |
| | Raynaud's phenomenom | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Vision disorders | Conjunctivitis | 2 | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 0 | 2 |
| | Lacrimation abnormal | 5 | 2 | 0 | 0 | 1 | 8 | 13 | 1 | 0 | 3 |
| | Vision decreased | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

pts, patients; CTC, common toxicity criteria

are depicted in Table 3. 2 patients experienced febrile neutropenia.

## 4. Discussion

Oral fluoropyrimidines are known to be a convenient alternative to the conventional intravenous administration of 5-FU. The oral route is preferred by most patients, with a potentially improved therapeutic index and possible pharmacokinetic advantages. The PK/PD results of this study will be described separately.

S-1, which combines the classic oral 5-FU-prodrug, tegafur, with two modulating agents, was designed to improve the antineoplastic activity while reducing the common gastrointestinal side-effects of fluoropyrimidine treatment. As the prolonged oral administration mimics the continuous infusion of 5-FU, side-effects such as diarrhoea, stomatitis, myelosuppression or skin toxicity were expected, which was confirmed by the phase I and II data [21,22].

Initially, S-1 was used as a single daily oral administration in Japan, and doses in the range of 25–200 mg total dose have been studied, with up to two dosings per day. Registration in Japan has been obtained following the observation of high response rates in Japanese patients: Sugimachi and colleagues gave twice 50–75 mg/day orally (p.o.) (days 1–28 every week (q-w)) in 31 (of which 9/28 evaluable were pretreated) patients and achieved a 54% response rate (CI: 38–68) [11]; Koizumi and colleagues administered 2×40–60 mg/day p.o. (days 1–28 q6w) in 51 non-pretreated patients and obtained 44% responses (CI: 30–59) [12]; Sakata and colleagues gave 2×40–60 mg/m$^2$ p.o. (days 1–28 q6w) in 51 non-pretreated patients and obtained 49% responses (CI: 36–62) [13].

The present study was performed in various European institutions; the initial dose of 40 mg/m$^2$ twice daily had to be reduced due to the incidence and severity of non-haematological toxicity in this and a parallel phase II trial in advanced colon cancers (mainly diarrhoea) [21].

At the 35 mg/m$^2$ starting dose, which we found to be much more manageable in our patients, one CR and five PR were obtained to achieve a response rate of 26% (90% CI 12–45) in the intent-to-treat population. All the responses were confirmed by an independent review. This indicates that S-1 achieves objective responses in untreated advanced gastric cancer patients, with a median duration of response of 223 days, and a median time to progression of 140 days.

S-1 was originally designed to decrease the gastrointestinal toxicity associated with the use of an oral fluoropyrimidine prodrug.

Table 3
Haematological toxicity: maximum CTC gradings per course (regardless of cause)

| Item | Starting dose level 40 mg/m$^2$ Grades ($n=38$ courses) 1 | 2 | 3 | 4 | Total | Starting dose level 35 mg/m$^2$ Grades ($n=78$ courses) 1 | 2 | 3 | 4 | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Anaemia | 8 | 28 | 0 | 0 | 36 | 40 | 29 | 4 | 1 | 74 |
| Thrombocytopenia | 7 | 3 | 1 | 1 | 12 | 10 | 1 | 5 | 3 | 19 |
| Leucopenia | 7 | 6 | 1 | 0 | 14 | 29 | 9 | 1 | 0 | 39 |
| Neutropenia | 5 | 7 | 3 | 1 | 16 | 18 | 12 | 1 | 1 | 32 |

At 40 mg/m$^2$, the total number of grade 3-4 toxicities of any kind amounted to 11 events for 7 patients and 38 courses. The incidence of diarrhoea was high, with 5 patients out of 7, of which 1 had a grade 3 and 1 a grade 4. Even if in this study the treatment seemed feasible, the dose was reduced for the rest of the trial, because there was simultaneously an impressive incidence of diarrhoea in metastatic colon cancer patients treated in a parallel phase II study with the same schedule as in our group [21].

At 35 mg/m$^2$, the overall safety was clearly improved, with a total of 12 non-haematological and 16 haematological grade 3-4 events for 78 courses in 23 patients. Diarrhoea was less, with 12 patients without diarrhoea versus 8 with grade 1-2 only, and 3 patients with a grade 3; no grade 4 diarrhoea was observed.

A dose reduction was required in 6 patients in the second course. The overall incidence of febrile neutropenia was low (2 cases).

For HFS, a case of a patient with a complete response was previously reported in Ref. [19]. This patient had a grade 3 HFS, beginning at course 4 with a grade 1, then worsening at course 7 to a grade 2, and at course 12 to a grade 3. 2 other cases with grade 1 HFS were observed.

According to the safety database of the manufacturer of S-1, Taiho Pharmaceuticals, HFS has been observed in just 7 out of 2280 mainly Asian patients (0.3%) treated with this compound, which is now commercially available as in Japan (data on file). However, we have seen the same symptoms in 3 out of 30 Caucasian patients with gastric cancer. There seemed to be a correlation between HFS and ocular toxicity. Interestingly Christophidis and colleagues [23] found 5-FU only to be present in the lacrimal fluid of patients with ocular toxicity, but not in the tears of symptom-free patients, which might reflect the pathogenetic mechanism of ocular toxicity in 5-FU-treated patients. In the literature, there were no data available on the incidence of HFS and ocular toxicity.

The treatment with the oral modulated fluoropyrimidine S-1 in non-pretreated advanced gastric cancer is safe at the dose of 35 mg/m$^2$ twice daily, and results in an appreciable rate of objective confirmed responses in European patients. However, the toxicity profile in this study seemed to be different from the Japanese studies, with more diarrhoea and HFS, and less myelotoxicity. This might be due to the use of a different administration schedule and/or to genetic differences between the Asian and Caucasian populations, requiring different rates of tegafur, oteracil and gimeracil in either population.

Combinations of S-1 with cisplatin or irinotecan and cisplatin are now being actively explored in Japan, based on the synergism of those agents in preclinical models. In Japan, S-1 has become one of the standard agents for the treatment of gastric cancer.

## Acknowledgements

We want to thank Drs. Droz (Lyon), Favre (Marseille), Oliveira (Lisbonne), Vermorken (Antwerp) for including one patient each; Dr. Dromain (Villejuif) for reviewing the responses and Mrs. G. Niezgodzki for her technical assistance and I. Tinet for preparing and typing the manuscript. We would like to acknowledge research support from TAIHO Pharmaceuticals, Japan.

## References

1. Karpeh MS, Kelsen DP, Tepper JE. Cancer of the stomach. Section 3 p 1092. In De Vita VT, Hellman S, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology,* 6th edn. Lippincott Williams Wilkins, 2001.
2. The Gastro-intestinal Tumor Study group. Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. *Cancer* 1982, **49**, 1116–1122.
3. Serlin O, Keehn RJ, Higgins GA, *et al.* Factors related to survival following resection for gastric carcinoma; analysis of 903 cases. *Cancer* 1977, **40**, 1318–1329.
4. Douglass HO, Nava HR. Gastric adenocarcinoma: management of the primary disease. *Semin Oncol* 1985, **12**, 32–45.
5. Kelsen D. Chemotherapy of gastric cancer: a review. *Israel J Med Sci* 1988, **24**, 557–561.
6. Shirasaka T, Shimamato Y, Oshimo H, *et al.* Development of a novel form of oral 5-fluorouracil derivative directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* 1996, **7**, 548–557.
7. Kimura K, Suga S, Shimaji T, *et al.* Clinical basis of chemotherapy for gastric cancer with uracil and 1-(2′-tetrahydrofuryl)-5-fluorouracil. *Gastroenterol Jpn* 1980, **15**, 324–329.
8. Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res* 1993, **53**, 4004–4009.
9. Takechi T, Nakano K, Uchida J, *et al.* Antitumor activity and low intestinal toxicity of S-1, a new oral fluoropyrimidine, in experimental tumor models in rats. *Cancer Chemother Pharmacol* 1997, **93**, 205–211.
10. Taguchi T, Inuyama Y, Kanamaru R, *et al.* Phase I study of S1. *Gan To Kagaku Ryoho* 1997, **24**, 2253–2264.
11. Sugimachi K, Maehara Y, Horikoshi N, *et al.* An early phase II study of oral S1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. *Oncology* 1999, **57**, 202–210.
12. Koizumi W, Kurihara M, Nakano S, *et al.* Phase II study of S1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. *Oncology* 2000, **58**, 191–197.
13. Sakata Y, Ohtsu A, Horikoshi N, *et al.* Late phase II study of novel oral fluoropyrimidine anticancer drug S1 (1M tegafur-0.4M gimestat-1M otastat potassium) in advanced cancer patients. *Eur J Cancer* 1998, **34**, 1715–1720.
14. Ohtsu A, Baba H, Sakata Y, *et al.* Phase II study of SI, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. *B J Cancer* 2000, **83**, 141–145.
15. Taguchi T, Morimoto K, Horikoshi N, *et al.* An early phase II study of S1 in patients with breast cancer. *Gan To Kagaku Ryoho* 1998, **25**, 1035–1043.
16. Inuyama Y, Kida A, Tsukuda M, *et al.* Early phase II study of S1 in patients with advanced head and neck cancer. Japan. *Gan To Kagaku Ryoho* 1998, **25**, 1151–1158.

17. Van Groeningen CJ, Peters GJ, Schornagel JH, *et al*. Phase I clinical and pharmacokinetic study of oral S1 in patients with advanced solid tumors. *J Clin Oncol* 2000, **18**, 2772–2779.
18. Gehan EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. *J Chronic Diseases* 1961, **13**, 346–353.
19. Schöffski P, Chollet P, Ganser A, *et al*. Complete response of a gastric primary after a short but toxic course of S1. *Ann Oncol* 1999, **10**, 1117–1120.
21. Vermorken JB, Schöffski P, Schellens J, *et al*, for the EORTC Early Clinical Studies Group (ECSG)/NDDO Oncology (supported by Taiho Pharmaceuticals). S-1 in metastatic colorectal cancer (CRC): interim analysis of an early phase II study. *Ann Oncol* 2000, **11**(Suppl. 4), 60.
22. Van Groeningen CJ, Peters GJ, Schornagel JH, *et al*. Phase I clinical and pharmacokinetic study of oral S-1 in patients with advanced solid tumors. *J Clin Oncol* 2000, **18**, 2772–2779.
23. Christophidis N, Vajda FJ, Lucas I, *et al*. Ocular side effects with 5-fluorouracil. *Aust NZ Med* 1979, **9**, 143–144.