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ORIGINAL ARTICLE

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# Alternate-day oral therapy with TS-1 for advanced gastric cancer

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**Abstract**
***Background.*** TS-1 (1 M tegafur-0.4 M 5-chloro-2,4-dihydroxypyrimidine-1 M potassium oxonate) has a high single-agent response rate, of more than 40%, for gastric cancer; however, the recommended regimen of 4 weeks of administration interrupted by 2 weeks of drug withdrawal frequently causes adverse effects. The alternate-day dosage of pyrimidine fluoride anticancer drugs could reduce their adverse effects without compromising their effects. We attempted an alternate-day therapy with TS-1 aiming at the avoidance of adverse effects and significantly longer duration of administration.
***Methods.*** We observed patients for clinical effects and adverse effects under alternate-day dosage of TS-1, and determined blood 5-fluorouracil (FU) levels. The judgment of clinical effects was based on the New Guidelines to Evaluate the Response to Treatment in Solid Tumors (RECIST), whereas the evaluation of adverse effects was based on the National Cancer Institute NCI-common toxicity criteria (CTC).
***Results.*** In 72 (78%) of 92 patients, the TS-1 regimen was converted to the alternate-day dosage because of adverse effects. Twenty patients were treated with the alternate-day dosage regimen from the start because of the fear of adverse effects. The alternate-day dosage was clinically effective, as 28 of 34 patients after relatively curative resection remained alive and free from recurrence. The median survival time of 58 patients after noncurative resection or with unresectable or recurrent cancer was 332 days. Fifty-three percent of these 58 patients achieved partial response and stable disease of more than 12 weeks' duration. We followed time-dependent changes in blood 5-FU levels in 36 of the patients on alternate-day therapy, in whom TS-1 had been administered daily before being administered every other day. The trough level was significantly lower when TS-1 was administered on alternate days, and blood 5-FU reached a peak at sufficiently effective levels at 2 h even after administration on the alternate-day basis.
***Conclusion.*** This study demonstrated that, compared with daily administration, alternate-day administration of TS-1 reduces adverse effects, and simultaneously ensures effective blood levels and provides sufficient clinical effects.

**Key words** Advanced gastric cancer · Chemotherapy · TS-1 · Alternate-day therapy

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## Introduction

Great expectations have been placed on chemotherapy for patients with unresectable gastric cancer and those at risk for recurrence after gastric cancer surgery. We have introduced tegafur plus 5-chloro-2,4-dihydroxypyrimidine plus potassium oxonate, at a molar ratio of 1:0.4:1(TS-1) as a first-line drug, but have frequently encountered adverse effects precluding continuation of the drug after administering the recommended daily dosage for 4 weeks interrupted by 2 weeks of drug withdrawal (hereafter referred to simply as daily dosage). Based on the theory of Shirasaka et al.[1] and Shirasaka[2] that the alternate-day dosage of pyrimidine fluoride anticancer drugs can reduce their adverse effects without compromising their effects, we previously reported that the alternate-day dosage of TS-1 (hereafter referred to simply as alternate-day dosage) was effective in patients with gastric cancer complicated by obstructive jaundice which seemed to predispose to adverse effects.[3] In the present study, we observed patients for clinical effects and adverse effects under alternate-day dosage of TS-1, and determined blood 5-fluorouracil (FU) levels.

## Patients and methods

### Indications for TS-1 therapy

TS-1 therapy was indicated for (1) patients at risk of recurrence, i.e., those with cancer with serosal invasion and those after relatively curative resection for stage III or more advanced gastric cancer (curability B), (2) patients with noncurative resection (curability C), and (3) patients with recurrent or unresectable cancer. Patients had to be capable of oral ingestion, to show performance status 0–1, and be aged from 20 to 79 years.

### TS-1 administration

The chemotherapy was started with the recommended daily dosage for 4 weeks interrupted by 2 weeks of drug withdrawal. TS-1 was administered orally at 40 mg/m$^2$ twice a day after meals; for patients 76 years old or older, the dosage was reduced. When grade 2 or higher adverse effects appeared, or when grade 1 non-hematological adverse effects made patients unwilling to continue to receive chemotherapy, the TS-1 regimen was converted to an alternate-day dosage regimen (40 mg/m$^2$ twice a day every other day) with confirmation of improvement of blood tests and/or clinical symptoms after 2 weeks' rest. In patients with coexisting disease and those 76 years old or older, therapy was started with an alternate-day dosage regimen instead of the daily dosage regimen, because of the fear of adverse effects. Before conversion from daily to alternate-day dosage, informed consent was obtained from all patients under approval of the Ethics Committee of Jichi Medical School (no.01-51). The terminology used in this article is based on the *Japanese classification of gastric carcinoma*.[4] The judgment of clinical effects was based on the New Guidelines to Evaluate the Response to Treatment in Solid Tumors (RECIST),[5] whereas the evaluation of adverse effects was based on the National Cancer Institute common toxicity criteria (NCI-CTC).[6]

### Determination of blood levels before and after dosage conversion

Changes in blood levels during daily dosage were compared with those during alternate-day dosage. On the seventh day after the usual daily dosage of TS-1, blood samples were collected before and 2, 4, and 6 h after administration to determine blood 5-FU levels. After 1 week of drug withdrawal, the same dose of TS-1 was administered on alternate days and, on the fourteenth day (seventh alternate day), blood samples were collected at similar time intervals.

### Judgment of therapeutic effects

Curability B patients were observed for recurrence and time to progression (TTP). Patients with curability C, recurrence, or unresectable gastric cancer were observed for the response rate, TTP, and median survival time (MST) as the best overall response, and the effectiveness was judged in patients achieving partial response (PR) and stable disease (SD) of more than 12 weeks' duration.

**Table 1.** Patients treated with TS-1 administration

| | No. of cases |
|---|---|
| Conversion to "alternate-day" | 72 |
| "Alternate-day" from the start | 20 |
| Continuation of "daily" | 23 |
| | 115 |

TS-1, 1 M tegafur-0.4 M 5-chloro-2,4-dihydroxypyrimidine-1 M potassium oxonate

## Results

Between 2000 and October 2003, we treated a total of 115 patients, consisting of 77 postoperative patients (35 curability B patients and 42 curability C patients), 15 patients with recurrence, and 23 patients with unresectable cancer. Therapy was started with daily dosage in 92 patients, but 72 (78%) did not wish to continue to receive chemotherapy because of grade 1 or higher adverse effects, and were converted to the alternate-day dosage of TS-1. Twenty patients (elderly or having coexisting disease) were administered TS-1 on alternate days from the start. Only 23 patients continued to be treated with daily dosage with no or minimal adverse effects (Table 1).

The adverse effects of daily dosage were classified as grade 1 in 36 patients (50%), grade 2 in 33 patients (46%), and grade 3 in 3 patients (4%) (Table 2). TS-1 therapy frequently caused symptomatic adverse effects (in 85% [61 of 72] patients), and made patients unwilling to continue to receive therapy. After conversion to the alternate-day dosage, grade 2 dermatitis and diarrhea persisted in 2 patients, and grade 1 leukopenia, nausea, diarrhea, pigmentation, or vomiting persisted in 5 of the 72 patients. In the remaining patients, adverse effects disappeared after conversion. As a result, in 72 patients, alternate-day chemotherapy was endured for a mean period of 272 days, while daily therapy had lasted only for 47 days on average. The completion rates of three courses of TS-1 therapy with daily and alternate-day dosage (total dose of 8400 mg) were 13% (9/72) and 56% (40/72) ($P < 0.05$, $x^2$ test), respectively, indicating a sufficient dose and dosage period without the appearance of adverse effects (Fig. 1).

The time course of changes in blood 5-FU levels showed that blood 5-FU levels before TS-1 administration in patients on alternate-day therapy were significantly lower (2.1 ng/ml) than those in patients on daily therapy (10.4 ng/ml; $P < 0.0001$, Student's-$t$ test), and that the blood concentration of 5-FU reached a peak at effective levels of 50–100 ng/ml at 2 h after administration during daily or alternate-day therapy, gradually decreasing over the next 6 h (Fig. 2).

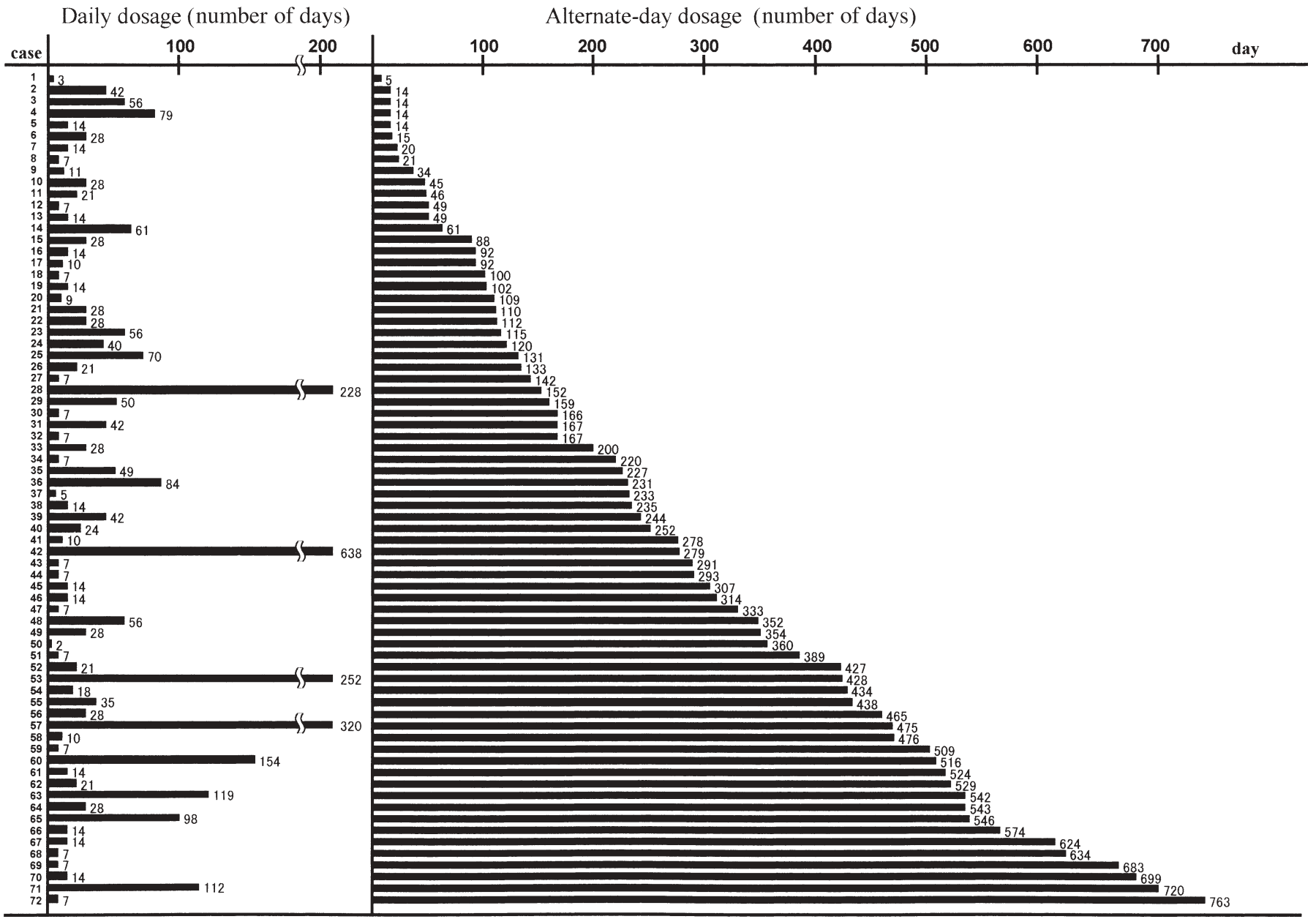


**Fig. 1.** Comparison of medication periods between daily and alternate-day administration ($n$ = 72). The mean periods of administration were daily: Alternate-day, 47:272 days. The completion rates of three courses (total dose of 8400 mg) of TS-1 (1 M tegafur-0.4 M 5-chloro-2,4-dihydroxypyrimidine-1 M potassium oxonate) therapy were: daily, 13% (9/72) and alternate-day, 56% (40/72; $P < 0.05$)

**Table 2.** Toxicities in patients treated with TS-1 ($n$ = 72)

| | Daily dosage | | | | Alternate-day dosage | | | |
|---|---|---|---|---|---|---|---|---|
| | G1, 36 (50%); G2, 33 (46%); G3, 3 (4%) NCI-CTC grade | | | | G1, 5 (7%); G2, 2 (3%) NCI-CTC grade | | | |
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Leukopenia/Neutropenia | 5 | 11 | 0 | 0 | 1 | 0 | 0 | 0 |
| Anemia | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Liver dysfunction | 5 | 4 | 1 | 0 | 0 | 0 | 0 | 0 |
| Renal dysfunction | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| General fatigue | 14 | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| Diarrhea | 12 | 7 | 1 | 0 | 1 | 1 | 0 | 0 |
| Pigmentation/dermatitis | 12 | 5 | 1 | 0 | 1 | 1 | 0 | 0 |
| Nausea/vomiting | 11 | 4 | 0 | 0 | 2 | 0 | 0 | 0 |
| Appetite loss | 9 | 5 | 0 | 0 | 0 | 0 | 0 | 0 |
| Stomatitis | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Taste disorder | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Herpes zoster | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Others | 5 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

Some patients had more than one toxicity
NCI-CTC, National Cancer Institute common toxicity criteria; G, grade

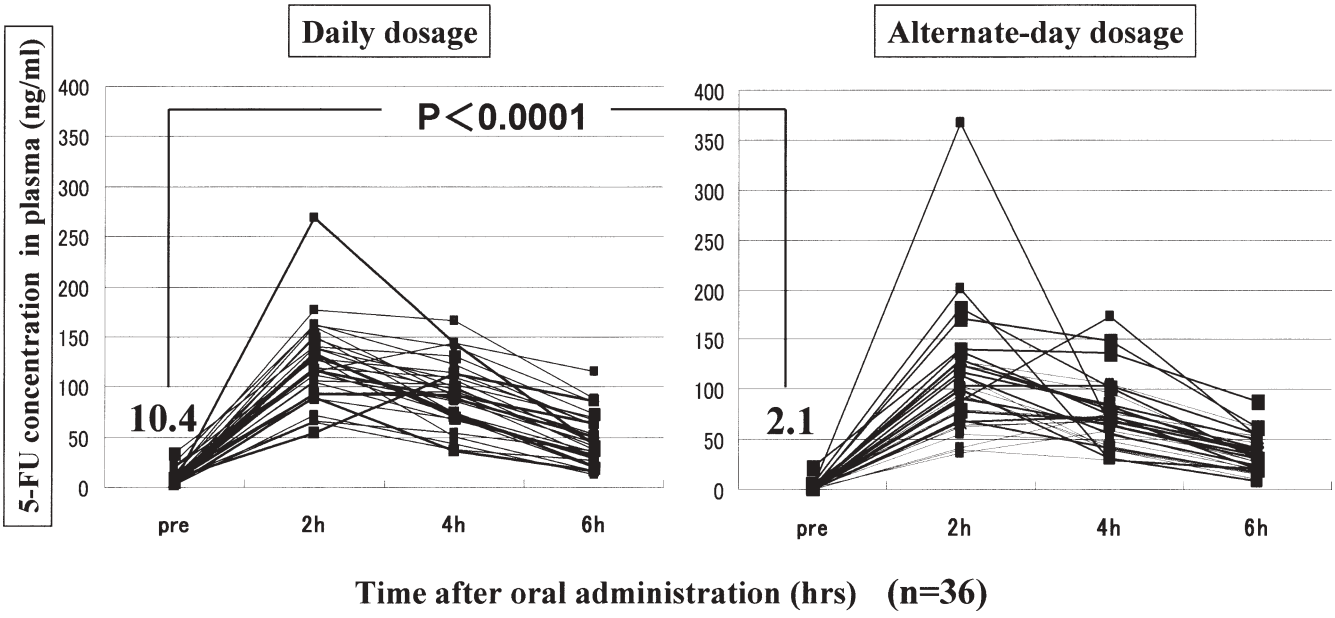


**Fig. 2.** Time-dependent changes in blood 5-fluorouracil (*5-FU*) levels with TS-1 administration ($n$ = 36). Although the trough level in patients on alternate-day dosage was significantly lower, at 2.1 ng/ml, than the level of 10.4 ng/ml in patients on daily dosage ($P < 0.0001$), blood 5-FU reached a peak at effective levels 2 h after administration on alternate-day dosage as well as daily dosage

Thirty-four (97%) of the 35 curability B patients received alternate-day administration; 6 (18%) of these 34 patients had recurrence, and 1 died. The median TTP of the 6 patients was 422 days (range, 247–821) days. The other 28 patients had no recurrence (follow-up period, 82–1097 days).

Thirty-five (83%) of the 42 curability C patients received the alternate-day therapy, and had an MST of 383 days (follow-up period, 118–1281 days). As the best overall response, 21 had SD, 14 had PD, and 17 (49%) died. The mean TTP in these 35 patients was 196 days. Thirteen (57%) of the 23 patients with unresectable cancer received the alternate-day therapy. PR, SD, and PD were encountered in 3, 2, and 8 patients, respectively. Twelve (92%) of these 13 patients died after an MST of 173 days. Ten (67%) of the 15 patients with recurrence after gastric cancer resection received the alternate-day therapy. As the best overall response, PR, SD, and PD were observed in 2, 3, and 5 patients, respectively, with an MST of 239 days.

The MST of the patients with no curative resection, or with unresectable or recurrent cancer was 332 days. Thirty-one (53%) of the 58 patients in these three groups receiving

**Table 3.** Response of patients treated with TS-1 alternate-day administration ($n$ = 92)

| | No. of cases | Alive without rec. | Rec. | (Dead) | TTP (days) | | | |
|---|---|---|---|---|---|---|---|---|
| CurB | 34 | 28 | 6 | (1) | 422 (range, 247–821) | | | |
| | | CR | PR | SD | PD | (Dead) | TTP (days) | MST (days) | PR + SD (%) |
| CurC | 35 | 0 | 0 | 21 | 14 | (17) | 196 | 383 | 21/35 (60%) |
| Unresectable | 13 | 0 | 3 | 2 | 8 | (12) | 110 | 173 | 5/13 (38%) |
| Recurrent | 10 | 0 | 2 | 3 | 5 | (8) | 161 | 239 | 5/10 (50%) |
| | 92/115 (80%) | | | | | | | 332 | 31/58 (53%) |

Reference, the New Guidelines to Evaluate the Response to Treatment in Solid Tumors (RECIST) (best overall response)
curB, after curative surgery; curC, after noncurative surgery; unresectable, unresectable gastric cancer; recurrent, recurrent cancer after surgery; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TTP, time to progression; MST, median survival time; rec., recurrence

**Table 4.** Response of patients treated with TS-1 daily administration ($n$ = 23)

| | No. of cases | Alive without rec. | Rec. | (Dead) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| CurB | 2 | 2 | 0 | 0 | | | | | |
| | | CR | PR | SD | PD | (Dead) | TTP (days) | MST (days) | PR + SD (%) |
| CurC | 6 | 0 | 0 | 4 | 2 | (3) | 70 | 274 | 4/6 (67%) |
| Unresectable | 9 | 0 | 1 | 3 | 5 | (6) | 90 | 210 | 4/9 (44%) |
| Recurrent | 6 | 0 | 0 | 2 | 4 | (2) | 32 | 245 | 2/6 (33%) |
| | 23 | | | | | | | 245 | 10/21 (48%) |

Reference, the RECIST guidelines (best overall response)
curB, after curative surgery; curC, after noncurative surgery; unresectable, unresectable gastric cancer; recurrent, recurrent cancer after surgery; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TTP, time to progression; MST, median survival time; Rec., recurrence

alternate-day therapy achieved PR and SD of more than 12 weeks' duration (Table 3).

The 23 patients treated by daily dosage alone consisted of 2 curability B patients, 6 curability C patients, 9 patients with unresectable cancer, and 6 with recurrent cancer; with a median number of 2.5 courses. The median survival time of the patients with noncurative resection, or unresectable or recurrent cancer after daily dosage was 245 days. Only 1 patient (11%) of the 9 patients with unresectable cancer achieved a PR. The other patients undergoing daily TS-1 therapy excluding the 2 curability B patients, had SD (9 patients) or PD (11 patients) (Table 4).

## Discussion

Studies have reported that chemotherapy for unresectable or recurrent cancer after surgery for advanced gastric cancer achieves a significantly longer survival time than best supportive care (BSC).[7–9] The main agents used are pyrimidine fluoride anticancer drugs,[10] among which TS-1 is an oral drug with a single-agent response rate of more than 40%,[1,11–13] contributing to good compliance; TS-1 is widely used as a first-line drug in Japan.

Instead of the conventional high-dose intravenous administration that aims at total cell killing,[14] the concept of how to continue drug administration safely and for long periods and ultimately prolong survival, without compromising quality of life (QOL), is now in the mainstream of chemotherapy for gastric cancer. TS-1 has achieved high single-agent response rates, of 44% to 49%, and a high MST, of 7 to 8 months.[11–13,15] However, in clinical practice, the recommended dosage regimen, consisting of 4 weeks of daily administration interrupted by 2 weeks of withdrawal, frequently causes not only bone marrow suppression but also non-hematological toxicities such as skin and digestive system disorders.[16,17] Therefore, an attempt to suppress the adverse effects and simultaneously maintain a prolonged antitumor effect should be pursued.

The rationale for alternate-day administration is as follows: 5-FU is a drug that is highly time-dependent, and it acts on S-phase cells, inhibiting DNA synthesis, thereby suppressing cell proliferation. Lipkin et al.,[18] in 1963, and Clarkson et al.,[19] in 1965, discovered a clear difference in the cell cycle between human normal and tumor cells: the

normal cell cycle takes as short a time as 0.5 to 1.5 days, whereas the cell cycle of tumor cells ranges from 5 to 7 days. Shirasaka et al.[1] and Shirasaka[2] focused their attention on this cell-cycle difference referring to the action of 5-FU. They expected that, because tumor cells would always be in contact with 5-FU during their S-phase, even if it was administered every other day, it would exert sufficient antitumor effects while normal cells could be withdrawn from the drug approximately every other day, resulting in a reduction in adverse effects.[1,2]

We started to administer TS-1 to 92 patients with advanced recurrent gastric cancer at a daily dosage, but 72 (78%) of them required withdrawal from the drug because of adverse effects. Based on the theory of Shirasaka et al.,[1] and Shirasaka[2] we attempted an alternate-day therapy, which resulted in the avoidance of adverse effects and significantly longer duration of administration in all patients except for 2 who had grade 2 adverse effects. In terms of clinical pharmacology, when blood 5-FU levels were determined in the same patient while on daily and alternate-day therapy, the trough level was significantly lower during the alternate-day therapy ($P < 0.0001$), suggesting that drug withdrawal contributes to the rescue of normal cells. During both daily and alternate-day therapies, blood 5-FU reached a peak at sufficiently effective levels at 2 h after administration. Thus, alternate-day therapy seems to provide sufficient antitumor effects, in accordance with the findings of Shirasaka et al.[1] and Shirasaka[2] that tumor cells are mostly exposed to 5-FU in the S-phase of the proliferation cycle.

The actual therapeutic effects of alternate-day TS-1 therapy were similar or superior to those in a late phase II clinical trial with daily dosage,[12,13] in that only 6 (18%) of the 34 curability B patients had recurrence, and 31 (53%) of the 58 patients with curability C, recurrence, or unresectable cancer achieved PR and SD of more than 12 weeks' duration, with an MST of 332 days.

## Conclusions

This study demonstrated that alternate-day TS-1 therapy ensured clinicopharmacolo-gically sufficient, effective blood levels, and provided clinical effects similar or superior to those of 4 weeks of daily administration interrupted by 2 weeks of withdrawal. Alternate-day TS-1 therapy holds promise as a dosage regimen that is expected to reduce adverse effects and simultaneously maintain antitumor effects.

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