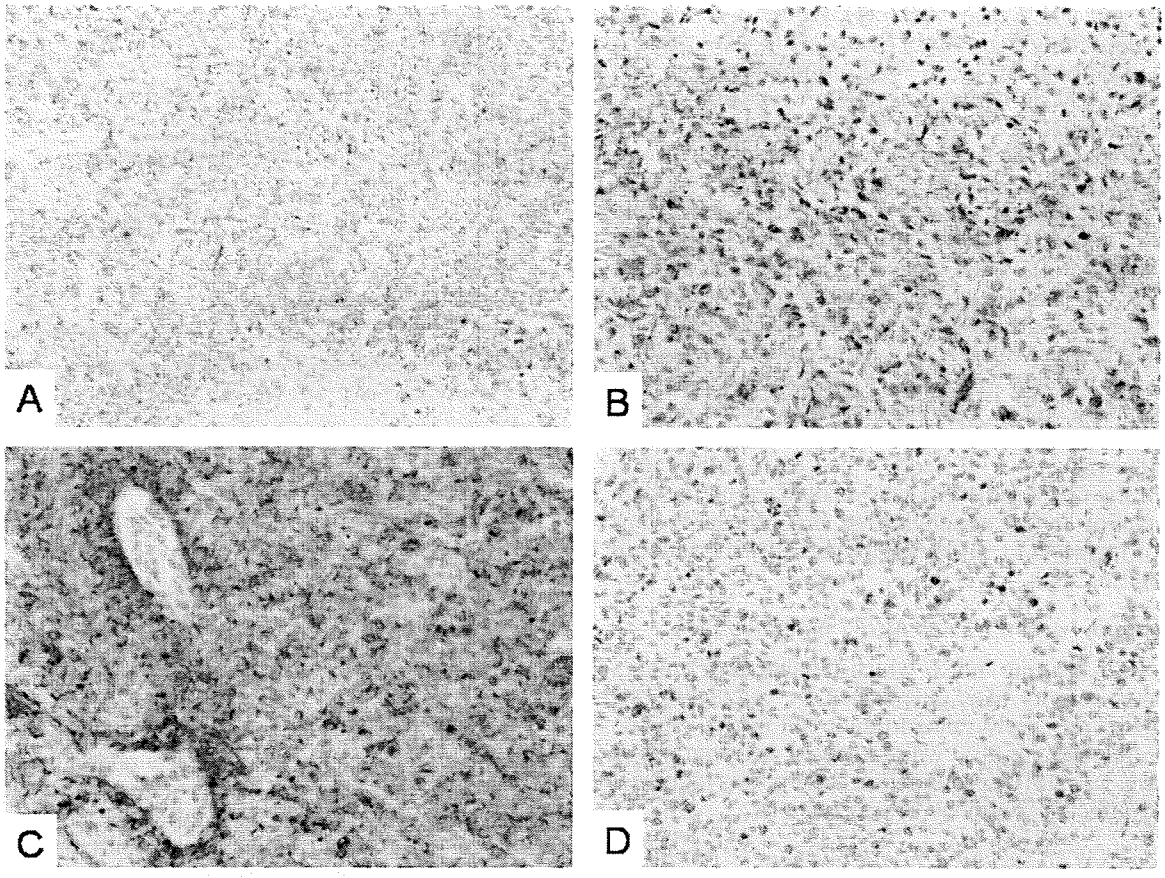


FIG. 2. Photomicrographs showing WT1 (A, B, and C) and MIB-1 (D) immunostaining. Representative WT1 immunostaining with scores of 2, 3, and 4 are shown in A, B, and C, respectively; MIB-1 immunostaining (D) in a specimen from the same case as panel C. Specimens were stained with antibody against WT1 protein (A, B, and C) or antibody against Ki 67 antigen (MIB-1) (D). Original magnification × 200.

very high compared with findings reported in chemotherapy studies, the disease control rate of 57.1% was favorable. The ability of WT1 vaccination to stabilize tumor growth might explain a good PFS of the patients treated with the vaccine. It should be emphasized that WT1 immunotherapy is less toxic than all of the chemotherapy treatments reported. Taken together, the patients in our study had a median PFS, 6-month PFS rate, and disease control rate that were comparable to those achieved using other chemotherapy regimens but with much less toxicity. These findings indicate that WT1 vaccination may be useful for the treatment of GBM.

In our study, WT1-specific CTL frequencies were higher in the PBMCs of patients with GBM than in those of healthy controls; this same phenomenon has been seen in other solid cancers.[19] The results, including good PFS and 6-month PFS rate and high stable disease rate, might be at least partly due to the high frequency of WT1-specific CTLs in the PBMCs of the patients prior to vaccination. Even in the responders, however, the CTL frequencies did not increase after vaccination. In our recent report,[19] we found a correlation between the clinical response and an increase in WT1-specific CTL frequencies in the PBMCs of cancer patients after vaccination. The correlation was clear in patients with leukemia, but it was not that clear in those with solid tumors (lung and breast cancer; unpublished data). Several cancer immunotherapy trials[2,13,14,21] have shown a poor correlation between clinical response and an increase in antigen-specific CTL frequencies. Germeau et al.[7] reported that high frequencies of the antigen-specific CTL were observed before vaccination and did not correlate the clinical response in solid cancers. They suggest that a spontaneous antitumor T-cell response that has become ineffective can be awakened by vaccination and contribute to tumor rejection. After the vaccination, CTLs in the responders might change qualitatively, but not quantitatively. The successfully activated CTLs could have more migratory ability, which would lead to the accumulation of CTLs in the brain.[12] These issues should be addressed by an intense analysis of the CTLs in WT1 vaccine-treated patients with GBM.

Immunohistochemical analysis showed that the patients with a high expression of WT1 protein in tumor specimens tended to respond well to WT1 vaccination. This finding suggests that the presence of high target antigen levels in the tumor cells plays an important role in the clinical responses. Taken together, both a high frequency of WT1-specific CTLs and a high WT1 protein expression level in tumor tissues may be needed for good clinical response to WT1 vaccination.

Under normal conditions, no lymphocytes are present in the brain parenchyma. However, tumor-infiltrating lym-

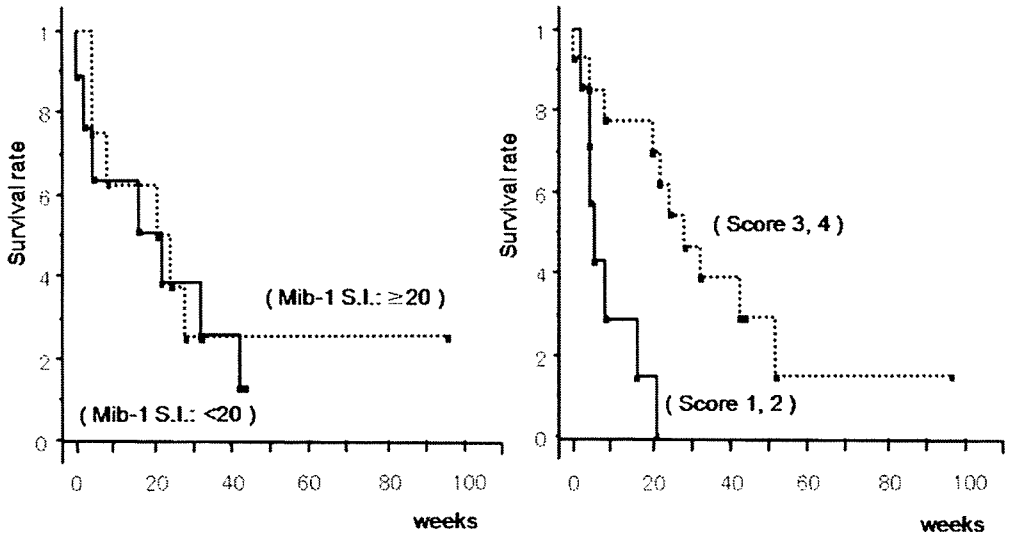


FIG. 3. *Left:* Kaplan–Meier curves for PFS after initial WT1 vaccination for patients with recurrent GBM classified by MIB-1 staining index (S.I.) determined by means of immunohistochemical analysis. The *solid line* indicates cases with an MIB-1 staining index of < 20%, and the *dotted line* indicates cases with an MIB-1 staining index of ≥ 20%. No statistical difference in PFS was observed between the 2 groups. *Right:* Kaplan–Meier curves for PFS after initial WT1 vaccination of patients with recurrent GBM classified by WT1 expression level. The *solid line* indicates cases with low WT1 expression on tumor cells (Score 1 or 2), and the *dotted line* indicates cases with high WT1 expression on tumor cells (Score 3 or 4). Cases with scores of 3 or 4 were associated with better PFS than cases with scores of 1 or 2 ($p = 0.002$).

phocytes are found in and around the tumors in 35–80% of patients with malignant glioma;[5] this may indicate that tumor-specific CTLs would be available to attack the tumor. It has also been reported that immunosuppressive mechanisms, such as the existence of regulatory T cells,[6] hamper CTL function. Thus, the combination of a cancer vaccine with other modalities to inhibit immunosuppressive mechanisms may be useful for improving the efficacy of the vaccine.

It is probable that some cancer patients treated with cancer vaccines can survive long-term without remarkable tumor regression. On the other hand, their tumors could be stabilized or could regress following a temporary increase in size after vaccination since, in general, immunotherapy does not act as quickly as chemotherapy. In fact, some patients in the stable disease group in this study survived for a long time without the treatments achieving partial response. In Case 8, a decrease in tumor size, although it did not reach the partial response level, was observed 7 months after the initial WT1 vaccination. Furthermore, in some of the patients whose clinical response was classified as progressive disease (Cases 3 and 9), tumor stabilization was induced by WT1 vaccination at a later time during the trial. Therefore, one has to consider whether RECIST, which is the gold standard for evaluating the response of solid tumors to cancer chemotherapy, is suitable for evaluating the clinical response to cancer vaccine treatment.[18]

The mechanisms of tumor escape from immune recognition/destruction are thought to be multifactorial. They include: downregulation of major histocompatibility complex Class I molecules, loss of tumor antigens, defective death receptor signaling, lack of costimulation, and the production of immunosuppressive cytokines and suppressive cells.[1]

Given the many different potential mechanisms, combination therapy strategies that use several treatment modalities could include sequential chemotherapy, radiotherapy, and immunotherapy protocols; these will need to be considered.[27]

## Conclusions

In HLA-A*2402–positive patients with GBM, immu-

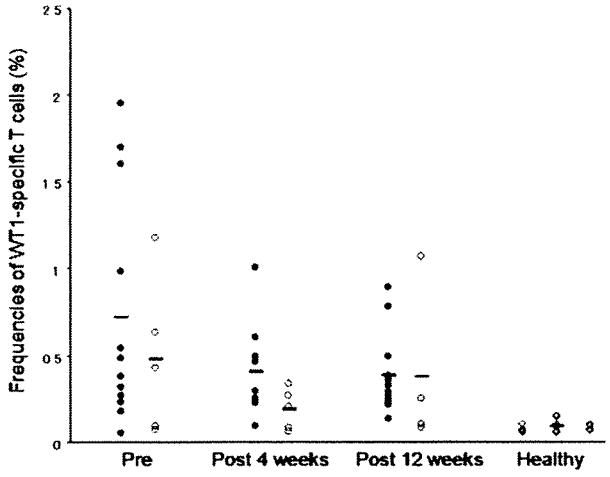


FIG. 4. Graph showing the frequencies of WT1-specific CTLs before WT1 vaccination, 4 and 12 weeks after WT1 vaccination, and in healthy controls. Patients with controlled disease (partial response or stable disease, *closed circles*) as well as those with uncontrolled disease (progressive disease, *open circles*) had a higher frequency of WT1-specific CTLs during the entire evaluation period than healthy controls *(diamonds)*. The *horizontal bars* indicate mean frequencies.

notherapy with HLA-A*2402–restricted, modified 9-mer WT1 peptide vaccination had disease-stabilizing, as well as disease progression–inhibiting, effects that were equal or superior to those of chemotherapy, with systemic toxicity that was much less than that of chemotherapy and thus allowed the vaccinations to be given for a long time. The WT1 protein is considered to be one of the most promising tumor antigens, since injection of a single WT1 peptide type can induce a clinical response. This is another advantage of the vaccine—one does not need to choose a suitable combination of peptides in the laboratory before vaccination. Compared with dendritic cell therapy, WT1 vaccination is simple. The use of a more suitable adjuvant, such as *Mycobacterium bovis* bacillus Calmette–Guérin cell wall skeleton (BCG-CWS),[16] or combination therapy involving vaccination[10] and other modalities may further enhance the clinical usefulness of this treatment for patients with GBM.

### Disclaimer

The authors have no conflicts of interest related to this paper.

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ORIGINAL ARTICLE

# Capecitabine and paclitaxel combination chemotherapy for inoperable or recurrent breast cancer: a phase I dose-finding study by the Kinki Breast Cancer Study Group

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## Abstract

*Background* The combination of capecitabine and paclitaxel (XP) has demonstrated synergistic antitumor activity in preclinical models. Three-weekly XP regimens have demonstrated excellent efficacy in phase II and III trials in metastatic breast cancer. We conducted a dose-finding study to identify the recommended 4-weekly XP regimen in patients with inoperable or recurrent breast cancer for phase II evaluation.

*Methods* Eligible patients had inoperable or recurrent breast cancer previously treated with chemotherapy (but not capecitabine or paclitaxel) in the (neo)adjuvant or metastatic setting. Each 4-week treatment cycle consisted of escalating doses of capecitabine (628 or 829 mg/m$^2$ twice daily [b.i.d.] on days 1–21) and paclitaxel (80 or 90 mg/m$^2$ on days 1, 8, and 15). Dose-limiting toxicities (DLT) were evaluated during the first two cycles.

*Results* Nine patients were treated. At dose level 1 (capecitabine 628 mg/m$^2$ b.i.d. plus paclitaxel 80 mg/m$^2$), one patient experienced a DLT (grade 3 non-hematologic toxicity). There were no further DLTs at dose level 1 or 2. Although the MTD was not reached, dose level 2 (capecitabine 829 mg/m$^2$ b.i.d., days 1–21, plus paclitaxel 80 mg/m$^2$, days 1, 8, and 15, every 28 days) is recommended for phase II evaluation, taking into consideration the single-agent doses used in Japan and the doses identified in Western studies of 3-weekly XP. The overall response rate was 44%; all patients treated at dose level 2 achieved a partial response.

*Conclusions* This 4-weekly XP regimen was well tolerated, active in patients with pretreated advanced breast cancer, and could be given as outpatient treatment. These results are consistent with findings of phase II and III trials evaluating 3-weekly regimens, and indicate that further investigation of a 4-weekly XP regimen is warranted.

**Keywords** Metastatic breast cancer · Capecitabine · Weekly · Paclitaxel · Phase I

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## Introduction

Anthracycline-containing regimens, such as doxorubicin and cyclophosphamide (AC), cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF), and 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), are highly active and widely used as primary systemic therapy (neoadjuvant or adjuvant), reducing the risks of recurrence and death compared with non-anthracycline-containing regimens [1]. Nevertheless, most patients develop metastatic disease. Further anthracycline therapy is frequently not possible because of the increased risk of cardiotoxicity, and the benefit of re-exposure to anthracyclines is unclear. Consequently, the search for new, more effective treatments for metastatic breast cancer (MBC) is ongoing.

The taxanes, including paclitaxel, are among the most active agents for the treatment of MBC [2–6] and are increasingly being used in the adjuvant setting for high-risk patients. In a Japanese study, paclitaxel produced a 33% response rate in anthracycline-pretreated patients with advanced or metastatic disease [7]. Results of the CALGB 9840 trial indicate that weekly paclitaxel is more effective than a 3-weekly schedule, resulting in a significantly higher response rate (40 vs. 28%, respectively; OR = 1.61, $P = 0.017$) and longer time to progression (adjusted hazard ratio = 1.45, $P = 0.0008$; median = 9 vs. 5 months, respectively), although the trend towards improved overall survival with the weekly regimen did not reach statistical significance [8]. Early results from the Anglo-Celtic IV trial, presented at ASCO 2007, support these findings [9]. The administration schedule of paclitaxel also affects the safety profile, with less myelosuppression but more neurotoxicity seen with the weekly regimen [8, 10]. In Japan, weekly taxane monotherapy is currently introduced as the standard therapy after anthracycline failure. We have previously reported the antitumor activity of weekly paclitaxel in docetaxel-resistant MBC [11].

The oral fluoropyrimidine capecitabine, which was created in the Chugai Pharmaceutical Kamakura Research Laboratories (at that time the Nippon Roche KK, Research Center), generates 5-fluorouracil preferentially at the tumor site through exploitation of the significantly higher concentration of thymidine phosphorylase (TP) in tumor versus normal tissue [12]. Capecitabine monotherapy has demonstrated consistently high activity and excellent tolerability in anthracycline- and/or taxane-pretreated MBC [13–17] and in the first-line setting [18–21]. The high single-agent activity and good tolerability of capecitabine make it an attractive combination partner. Furthermore, in preclinical models, upregulation of TP by agents such as docetaxel, paclitaxel, and cyclophosphamide results in synergistic antitumor activity when co-administered with capecitabine [22, 23]. In the clinical setting, the combination of capecitabine and docetaxel in anthracycline-pretreated MBC significantly improves response rate, time to progression, and overall survival compared with docetaxel alone [24]. In addition, results of a randomized, phase II trial presented at ASCO 2006 indicated that in the first-line setting, the combination of capecitabine and docetaxel significantly improved response rate, time to progression, and overall survival compared with sequential docetaxel followed at progression by capecitabine [25]. Several phase II and III trials have demonstrated that the combination of capecitabine and paclitaxel (XP, with paclitaxel administered using a weekly or a 3-weekly schedule) is also highly active [26–30]. In a recently reported randomized, phase III trial, XP demonstrated similar efficacy to epirubicin plus paclitaxel, with median overall survival of 25.6 months and median progression-free survival of 12.0 months at interim analysis [30].

Previously reported clinical trials have evaluated XP administered using 3-weekly cycles, with capecitabine given according to the standard schedule used in Europe and the USA (capecitabine twice daily (b.i.d.) for 14 days followed by a 7-day rest period). In Japan, however, a 4-weekly regimen with capecitabine given on days 1–21 followed by a 7-day rest period has been investigated [31–33]. This regimen was selected for further development based on cutaneous effects observed in an early dose-finding study of a continuous regimen in Japanese patients [34]. Treatment with capecitabine monotherapy is covered by National Health Insurance only if administered using this 4-weekly schedule at a dose of 829 mg/m$^2$ b.i.d. As a result, a 4-weekly schedule is commonly adopted in clinical practice in Japan. Similarly, paclitaxel treatment for MBC typically consists of weekly administration of 80 mg/m$^2$ on days 1, 8, and 15 every 28 days. Therefore a 28-day XP combination regimen may be a valid alternative to the 21-day regimen developed in most Western countries.

## Patients and methods

### Study design

The primary objective of this multicenter, phase I, dose-finding study conducted by the Kinki Breast Cancer Study Group (KBCSG) was to identify the maximum tolerated dose of a 28-day regimen of capecitabine in combination with weekly paclitaxel in patients with advanced or recurrent breast cancer, and determine the recommended dose for a phase II study. Secondary objectives included estimation of the proportion of patients achieving a response or stable disease 6 months after treatment initiation and assessment of the safety profile. A standard 3 + 3 dose-escalation design was used.

The protocol was approved by the institutional review board at each center. The study was conducted in accordance with Good Clinical Practice Guidelines (Sixth International Conference on Harmonisation and the Declaration of Helsinki). All patients provided written informed consent.

## Eligibility criteria

Female patients with histologically or cytologically confirmed breast cancer and evidence of measurable metastatic disease using Response Evaluation Criteria in Solid Tumors (RECIST) were eligible for this study. Main inclusion criteria were: age 20–75 years, ECOG performance status 0 or 1, normal renal, hepatic, and hematologic function confirmed by a prestudy examination (white blood cell count $\geq$ 4,000/mm$^3$ and $\leq$12,000/mm$^3$, neutrophil count $\geq$ 2,000/mm$^3$, platelet count $\geq$ 100,000/mm$^3$, hemoglobin $\geq$ 9.0 g/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2.5 $\times$ upper limit of clinic normal (ULN), total bilirubin < 1.25 $\times$ ULN, serum creatinine < 1.5 $\times$ ULN, creatinine clearance > 50 ml/min), and no prior radiotherapy to the target lesion. At least 2 weeks must have elapsed since completing previous endocrine therapy and 4 weeks must have elapsed since completion of previous chemotherapy, radiotherapy, surgery, or treatment with an investigational new drug. Patients were ineligible if they had previously received a taxane or capecitabine.

## Treatment

Capecitabine was administered orally at a twice-daily dose of 628 mg/m$^2$ (dose level 1) or 829 mg/m$^2$ (dose levels 2 and 3) taken within 30 min after morning and evening meals, for 21 consecutive days. Paclitaxel was administered intravenously as a 60-minute infusion at a dose of 80 mg/m$^2$ (levels 1 and 2) or 90 mg/m$^2$ (level 3) on days 1, 8, and 15. These initial doses were selected based on the anticipated increase in both efficacy and toxicity compared with single-agent administration, as is usual in combination studies. Table 1 shows the dose–escalation scheme. Premedication prior to paclitaxel administration was mandatory and consisted of i.v. dexamethasone 20 mg, oral diphenhydramine hydrochloride 50 mg, and i.v. ranitidine 50 mg. If no hypersensitivity reactions occurred after the first dose of paclitaxel, the dexamethasone dose could be reduced to 8 mg from cycle 2 onwards at the discretion of the treating physician. If the first two cycles of XP combination therapy were well tolerated, patients could continue to receive combination therapy until disease progression or unacceptable toxicity.

**Table 1** Dose-escalation scheme

| Dose level | Paclitaxel days 1, 8.15 (mg/m$^2$) | Capecitabine days 1–21 (mg/m$^2$) b.i.d |
|---|---|---|
| −1 | 70 | 628 |
| 1 | 80 | 628 |
| 2 | 80 | 829 |
| 3 | 90 | 829 |

b.i.d. twice daily

## Dose–escalation scheme

The first cohort of three patients was treated at dose level 1. Dose-escalation decisions were based on the occurrence of dose-limiting toxicities (DLT) during the first two cycles. DLTs were defined as any of the following during the first two cycles of chemotherapy: (1) grade 4 leukopenia (<1,000/mm$^3$) or neutropenia (<500/mm$^3$) lasting for >4 days; (2) toxicity resulting in omission of two or more paclitaxel doses; (3) fever (>38.0°C) associated with grade 3 or 4 neutropenia (<1,000/mm$^3$) or clinical infection; (4) grade 4 thrombocytopenia (<25,000/mm$^3$); (5) grade 3 hand–foot syndrome [12]; (6) other grade 4 non-hematologic toxicity (excluding hair loss, nausea/vomiting, and anorexia); (7) toxicity resulting in a delay of >7 days before administration of the second or third cycle. Any events other than those described above could be classified as a DLT at the discretion of the data and safety monitoring committee.

If none of the three patients in a cohort experienced a DLT, three patients were to be treated at the next dose level. If one of the three patients experienced a DLT, three additional patients were to be treated at the same dose level. If no further DLTs occurred, three patients were to be treated at the next dose level. If a DLT occurred in two or more of a cohort of six patients, or two or more of a cohort of three patients, that dose level was to be defined as the maximum tolerated dose and the previous dose level was to be defined as the recommended dose.

## Study assessments

Adverse events were graded using the National Cancer Institute Common Toxicity Criteria (CTCAE v3.0). Details of all adverse events and laboratory abnormalities and their relationship to study treatment were to be recorded on the Case Report Form. Tumor lesions were measured at baseline and after every second cycle using RECIST.

## Results

### Patient characteristics

Between November 2003 and June 2005, nine women were enrolled, all of whom had previously received chemotherapy. Six received dose level 1 and three received dose level 2. Baseline characteristics are summarized in Table 2. XP was given as first-line chemotherapy for MBC in three patients, second-line therapy in five patients and third-line therapy in one patient.

### Tolerability

Table 3 shows all adverse events occurring in more than one patient during the first two cycles of therapy. Among the first cohort of three patients treated at dose level 1 (capecitabine 628 mg/m$^2$ b.i.d., paclitaxel 80 mg/m$^2$), one experienced grade 3 non-hematologic toxicity (peripheral neuropathy, malaise, muscle pain, difficulty in walking due to pelvic pain), meeting the criteria for DLT. Therefore, three additional patients were recruited to dose level 1. There were no further DLTs at this dose level. Three patients were enrolled to dose level 2, none of whom experienced any DLT. Hand-foot syndrome was observed at grade 1 intensity in two patients and grade 2 intensity in four patients. There were no grade 3 cases in any of the patients treated in this study and there was no evidence that concomitant use of paclitaxel exacerbated hand-foot syndrome.

When all three patients had completed combination treatment at level 2, tolerability was evaluated by the data and safety monitoring committee. The panel decided that as both capecitabine and paclitaxel had been administered at their full, Japanese regimen, single-agent doses (capecitabine 829 mg/m$^2$ b.i.d., paclitaxel 80 mg/m$^2$), and the dose intensity of level 2 exceeded the doses adopted in clinical trials of this combination in the USA, escalation to dose level 3 should not proceed. Consequently, the recommended regimen for phase II evaluation is capecitabine 829 mg/m$^2$ b.i.d. on days 1–21 in combination with paclitaxel 80 mg/m$^2$ on days 1, 8, and 15, both repeated every 28 days.

**Table 2** Baseline characteristics ($n$ = 9)

| | |
|---|---|
| Median age, years (range) | 55 (47–66) |
| ECOG performance status | |
| 0 | 4 |
| 1 | 5 |
| Menopausal status | |
| Premenopausal | 1 |
| Postmenopausal | 8 |
| Sites of metastases | |
| Liver | 6 |
| Lung | 3 |
| Pleura | 1 |
| Bone | 5 |
| Skin | 1 |
| Lymph node | 4 |
| Prior adjuvant chemotherapy | |
| None | 4 |
| CMF | 2 |
| Anthracycline | 2 |
| Oral 5-fluorouracil | 1 |
| Prior chemotherapy for MBC | |
| None | 3 |
| Anthracycline | 5 |
| Docetaxel | 1 |

*CMF* cyclophosphamide methotrexate 5-fluorouracil, *MBC* metastatic breast cancer

**Table 3** Adverse events occurring in more than one patient during the first two cycles of therapy

| | Level 1 ($n$ = 6) | | Level 2 ($n$ = 3) | |
|---|---|---|---|---|
| Capecitabine (mg/m$^2$ b.i.d., days 1–21) | 628 | | 829 | |
| Paclitaxel (mg/m$^2$, days 1, 8,15) | 80 | | 80 | |
| Grade | 2 | 3 | 2 | 3 |
| Hematologic | | | | |
| Leukopenia | 3 | 0 | 3 | 0 |
| Neutropenia | 0 | 1 | 3 | 0 |
| Non-hematologic | | | | |
| Anorexia | 0 | 0 | 1 | 0 |
| Nausea | 0 | 0 | 1 | 0 |
| Vomiting | 1 | 0 | 2 | 0 |
| Diarrhea | 0 | 0 | 2 | 0 |
| Constipation | 1 | 0 | 1 | 0 |
| Neurotoxicity (sensory) | 1 | 1 | 0 | 0 |
| Fatigue | 1 | 1 | 0 | 0 |
| Muscle pain | 0 | 1 | 0 | 0 |
| Arthralgia | 1 | 0 | 0 | 0 |
| Hand–foot syndrome | 3 | 0 | 1 | 0 |
| Alopecia | 2 | 0 | 0 | 0 |
| Dysgeusia | 0 | 0 | 2 | 0 |
| Hypertension | 0 | 0 | 1 | 0 |
| Desquamation | 0 | 0 | 2 | 0 |
| Laboratory | | | | |
| AST | 1 | 0 | 0 | 0 |
| ALT | 0 | 0 | 1 | 0 |

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase

Antitumor efficacy

Partial responses were confirmed in all three patients receiving dose level 2 and one of the two patients receiving dose level 1 as first-line therapy, giving an overall response rate of 44% (4/9 patients). The other patient receiving dose level 1 as first-line therapy achieved stable disease. Among the remaining four patients receiving dose level 1 as second- ($n = 3$) or third-line ($n = 1$) therapy, three-showed disease progression and one was not evaluable.

## Discussion

The 4-weekly XP schedule investigated in this study is well tolerated and active. We recommend a regimen of capecitabine 829 mg/m$^2$ b.i.d. on days 1–21 plus paclitaxel 80 mg/m$^2$ on days 1, 8, and 15, both repeated every 28 days, for phase II evaluation. Our results provide an early indication that our 4-weekly XP regimen is a valid alternative to the 3-weekly regimen used in other parts of the world.

In patients with less aggressive, asymptomatic, small-volume breast cancer following anthracycline- and/or taxane-containing (neo)adjuvant therapy, oral capecitabine monotherapy is considered an acceptable first-line therapy, enabling patients to maintain good quality of life. At disease progression, more intensive chemotherapy, including intravenous taxane therapy, may be considered.

In patients with more aggressive disease who require rapid reduction in tumor burden, the regimen offering the highest response rate should be considered. This strategy is important because if first-line therapy is ineffective, resulting in increased tumor volume, further treatment may be compromised because of extensive tumor growth, deterioration in general health, or worsening symptoms. This concept is supported by results of the randomized, phase III trial reported by O'Shaughnessy et al. [24], in which 35% of patients initially randomized to docetaxel received no further chemotherapy at progression, thus denying them the opportunity to benefit from other agents [35]. Further support comes from a randomized clinical trial comparing capecitabine and docetaxel combination treatment versus sequential administration of these two agents [25]. In this trial, response rate, progression-free survival, and overall survival were significantly superior in patients receiving combination versus sequential treatment. Similarly, the authors of the Mexican Oncology Group Study concluded that "when rapid response is the primary goal, patients should receive combination therapy (capecitabine plus taxane). If long-term outcomes and quality of life are more important, capecitabine followed by a taxane is an equally appropriate choice" [21].

The value of capecitabine/taxane combination regimens has been seen in numerous clinical trials [24–30, 36–38]. Phase I and II studies conducted in Europe and North and South America have explored different doses and schedules of XP. In several of these studies [28, 36, 38], a capecitabine dose of 1,000 mg/m$^2$ b.i.d., days 1–14 every 21 days, has been adopted. This dose was also used in combination with 3-weekly paclitaxel in the randomized phase III trial versus epirubicin/paclitaxel as first-line therapy for MBC [30]. The capecitabine dose recommended based on results of the present study provides a dose intensity of 8,699 mg/m$^2$/week, very similar to the 9,333 mg/m$^2$/week intensity in the studies using 1,000 mg/m$^2$ b.i.d. in a 3-weekly regimen. Interestingly, in the US Oncology phase II study reported by Blum et al. [29], the US phase II study reported by Gradishar et al. [27], and the randomized trial by the Mexican Oncology Study Group [21], the dose intensity was only 7,700 mg/m$^2$/week. This difference can probably be explained by regional differences in the tolerability of fluoropyrimidines that have recently become apparent. In an analysis of more than 3,000 patients treated with 5-fluorouracil- or capecitabine-based regimens for colorectal cancer, fluoropyrimidine therapy was least well tolerated in US patients and best tolerated in Asian patients [39]. Tolerability in European patients was intermediate. Thus, subtle differences in dose intensity may be appropriate when these differences are taken into account. Recently, a 2-weekly regimen with capecitabine given on days 1–7 every 14 days has been investigated in the USA [40], based on preclinical findings and mathematical modeling [41]. Although the average weekly dose delivered using this 7/7 schedule is no higher than with the conventional schedule, it is attracting some interest in the USA. Hand–foot syndrome and diarrhea remain the DLTs. The paclitaxel dose intensity in our study was identical to that used in the study by Susnjar et al. [36].

Both the randomized phase III trial of capecitabine plus 3-weekly paclitaxel [30] and the US phase II study investigating capecitabine plus paclitaxel on days 1 and 8 [29] demonstrated remarkable efficacy. Response rates were 52 and 55%, respectively, and median overall survival was 25.6 and 17 months, respectively. The slightly lower response rate in the present small study was to be expected given that most patients received XP in the second- or third-line setting in our study, contrasting with the first-line setting in the larger studies. Moreover, this Japanese study included only nine patients and was not designed to assess efficacy. Nevertheless, antitumor activity was evident.

To further assess the efficacy and tolerability of a 4-weekly XP schedule in Japanese patients, a multicenter, phase II trial (KBCSG 0609) has been initiated using the regimen identified in the present study.

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CLINICAL TRIAL REPORT

# A multicenter phase II study of biweekly paclitaxel and S-1 combination chemotherapy for unresectable or recurrent gastric cancer

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## Abstract

*Purpose* This Phase II study assessed the activity and safety of biweekly paclitaxel and oral S-1 as treatment for unresectable and recurrent gastric cancer. The maximum tolerated dose for this regimen had been established previously in a Phase I study performed in Japanese patients.

*Patients and methods* Chemotherapy was performed using two anticancer agents, S-1 and paclitaxel. Oral S-1 (80 mg/m$^2$) was administered twice a day after meals for two consecutive weeks from Day 1 to 14, followed by a 2 week recovery period; paclitaxel (120 mg/m$^2$) was administered intravenously, biweekly, on Days 1 and 15. The patient received cycles of this regimen every 4 weeks (q 28-day cycles). The primary end point was the response rate according to the Response Evaluation Criteria in Solid Tumors.

*Results* A total of 39 patients (median age, 65 years) were enrolled; 13 other patients were screened, but found to be ineligible. All patients had unresectable and recurrent gastric cancer. The most common treatment-related Grade 3/4 adverse events were neutropenia (37.5%), appetite loss, diarrhea, decreased sodium (each 5%), and anemia, increased alanine aminotransferase, general fatigue, and dizziness (each 2.5%). Almost all the patients experienced alopecia. Intent-to-treat analysis showed a response rate of 43.6%. With a median follow-up of 14 months (range 8–21 months), median survival was 256 days and the median time to progression was 4 months.

*Conclusion* A combination regimen of biweekly paclitaxel and oral S-1 was well tolerated and showed promising activity against unresectable and recurrent gastric cancer.

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**Keywords** Advanced gastric cancer · Phase II · Paclitaxel · S-1 · Chemotherapy

## Introduction

Gastric cancer is still one of the most common malignancies and a major leading cause of cancer-related death worldwide [1, 2]. Although patients in the early stages of gastric cancer have a good prognosis, those with advanced or unresectable disease are incurable, and for this group of patients the prognosis is poor.

Recently, some new regimens of combination chemotherapy have shown promising efficacy in advanced gastric cancer [3–5]. Several randomized studies have shown that these new combination chemotherapies have improved the quality of life and overall survival compared with the best supportive care [6–8]. Nevertheless, even with these promising regimens, the number of patients who benefit from treatment remains limited. In addition, because of interpatient differences with respect to efficacy and toxicity, there is no one regimen that stands out as better than the rest. Therefore, by designing new combination regimens and investigating their efficacy and safety in the clinical trial setting, it is hoped that a protocol with a clear clinical benefit may emerge.

Among these new anticancer agents, S-1 (Taiho Pharmaceutical Co Ltd, Tokyo, Japan) based combination chemotherapies have been popular in Japan. S-1 is a novel fluoropyrimidine derivative, which is composed of tegafur (FT); a prodrug of 5-fluorouracil (5-FU)), and two modulators, gimeracil (CDHP) and oteracil potassium (Oxo). Following the oral administration of S-1, the antitumor effect is achieved by the gradual conversion of FT to 5-FU. S-1 was designed to enhance the clinical utility of an oral fluoropyrimidine, but at the same time to be associated with reduced gastrointestinal toxicity [9–11]. S-1 monotherapy showed an overall response rate of 44% in the Phase II study [12]. Combination of S-1 and CDDP showed high activity and the response rate of this regimen was reportedly as high as 60%.

Paclitaxel (Bristol-Myers Squibb Co., Tokyo, Japan) is a taxane which is extracted from the bark of the Pacific yew and the needles of the English yew. It binds with high affinity to microtubules and enhances tubulin polymerization. This action inhibits the normal dynamic process of the cell's microtubule network resulting in the inhibition of mitosis and cell division [13, 14]. Paclitaxel's antitumor effect is derived from this inhibitory action. Monotherapy with paclitaxel is associated with an overall response rate of 28% in advanced gastric cancer patients [15]. Biweekly administration of paclitaxel has also succeeded in breast, lung and head and neck cancer, the merit of biweekly administration reportedly weakening the toxicity of paclitaxel while preserving its activity.

Therefore, it can be seen that S-1 and paclitaxel have different mechanisms behind their function and resistance, as well as non-overlapping toxicities. We developed this combination chemotherapy of S-1 and biweekly paclitaxel, and determined the maximum tolerated dose (MTD) in a Phase I study in Japanese patients with advanced gastric cancer [16]. We report here the results of a subsequent multicenter Phase II study with biweekly paclitaxel and oral S-1 combination chemotherapy as first-line treatment for recurrent and unresectable gastric cancer.

## Patients and methods

### Patients' eligibility

To be eligible for the study, patients had to have unresectable, histologically confirmed adenocarcinoma of the stomach. The extent of the tumor was evaluated with computed tomography (CT) or magnetic resonance imaging (MRI). The presence of at least one measurable lesion by the response evaluation criteria in solid tumors (RECIST) was required [17]. Patients were excluded if they had brain metastasis, large ascites or pleural effusion. Prior treatment for advanced gastric cancer, including the administration of paclitaxel, was an exclusion criterion, although patients who had received adjuvant therapy with fluorouracil were eligible provided more than 4 months had elapsed between the end of adjuvant therapy and registration on this study. All patients had to be aged between 20 and 80 years, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and life expectancy of 12 weeks; in addition, they had to be able to swallow tablets.

Pretreatment evaluation included complete medical history and physical examination, electrocardiography (ECG), complete blood count (CBC), serum chemistries and electrolytes, urinalysis, chest X-ray, and recording of concomitant medications. Patients were required to have adequate bone marrow, renal and hepatic function, defined as an absolute neutrophil count (ANC) of 2,000 $\mu L^{-1}$, a platelet count of 100,000 $\mu L^{-1}$, hemoglobin of 8.0 g/dL, serum creatinine of 1.5 mg/dL, and total bilirubin of 1.5 mg/dL. Patients were also required to have serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) levels of 2.5× the upper limit of normal (ULN) (3.0× the ULN in the presence of liver metastasis). Patients with serious arrhythmia or ischemic changes on the ECG were excluded. All patients gave written informed consent before enrolment and the study was approved by the ethics committees in each institution. The study conformed to the

principles of the Declaration of Helsinki and its subsequent amendments.

### Chemotherapy

Chemotherapy was performed using two anticancer agents, S-1 and paclitaxel. The MTD and DLT of this combination of biweekly paclitaxel and S-1 in advanced gastric cancer had been established previously in a Phase I study performed in Japanese patients [16]. Based on the findings from this earlier study, the recommended doses for this Phase II study with paclitaxel and S-1 were set at 120 and 80 mg/m$^2$, respectively [13]. Oral S-1 was administered twice a day, after meals, for two consecutive weeks from Day 1 to 14, followed by a 14-day recovery period. Paclitaxel was administered intravenously, biweekly on Days 1 and 15. Cycles were repeated every 28 days. The patient continued to receive cycles of this regimen until there was evidence of disease progression, the development of unacceptable toxicity in the investigator's opinion, or if the patient withdrew consent. Patients going off study were allowed to receive any second-line treatment.

### Evaluations of toxicity

Patients were monitored for CBC and serum chemistries every week during the first cycle. After the second cycle, they were monitored every 2 weeks. All adverse events were graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0). Dose modifications and treatment delays were performed as necessary according to the extent of hematological and organ toxicity. When a Grade 4 hematotoxicity or febrile neutropenia, or a Grade 3 non-hematotoxicity except alopecia, occurred during therapy, S-1 and paclitaxel were withheld and resumed at a reduced dose once the toxicity had resolved; all subsequent cycles were administered at the reduced dose. If treatment-related Grade 3 stomatitis or diarrhea occurred, only the S-1 dose was reduced. In cases of severe peripheral neuropathy, only the dose of paclitaxel was reduced. Treatment could be delayed for up to 2 weeks for hematological toxicities and/or other severe non-hematologic toxicities. If these toxicities had not resolved within 2 weeks after dose reduction, the administration of the study drugs was discontinued.

### Evaluation of response

Baseline CT or MRI scans of measurable lesions were carried out within 4 weeks of the start of study treatment. After every cycle of chemotherapy, patients received follow-up CT or MRI scans for assessment of response according to RECIST definitions [14]. The tumor size of all measurable lesions had to have been assessed by the first day of the next cycle. Complete response (CR) and partial response (PR) had to be confirmed at least 4 weeks after the first assessment. Imaging films of all assessable patients were also reviewed externally by an independent-review panel to confirm investigator-designed responses.

### Statistical considerations

The primary end point of this study was the overall response rate (ORR = CR + PR). Secondary end points were progression-free survival (PFS), overall survival (OS) and adverse events. The required number of patients for this trial was 34, calculated according to Fleming's single-stage design with a power of 80% and a significance level of 5%. In anticipation of 10% of patients being ineligible, we planned to enrol 38 patients. All eligible patients were included in the response, safety and survival analyses. Time to progression (TTP), defined as the time from study entry until documented tumor progression, and OS, defined as the time from study entry until death, were analyzed according to the Kaplan–Meier method.

## Results

### Patient characteristics

A total of 52 patients were registered at 20 centers between July 2003 and December 2005. Thirteen patients did not meet the entry requirements and therefore, 39 patients (33 males, 6 females) were finally enrolled into the study. Baseline characteristics are listed in Table 1. The median age was 65 years (range 37–79 years); 37 (95%) patients had ECOG PS 0 to 1, and 26 (65%) had multiple metastatic lesions involving two or more organ systems. Histological types of primary lesion were: tubular adenocarcinoma (52.5%), papillary adenocarcinoma (2.5%), poorly differentiated adenocarcinoma (35%), signet-ring cell carcinoma (7.5%) and mucinous adenocarcinoma (2.5%) (Table 1). Abdominal lymph nodes and the liver were the most common metastatic sites.

### Treatment administered

A total of 144 cycles of paclitaxel-S1 were administered, with a median of 3.7 per patient (range 2–8). Four patients (10%) had a dose reduction, for Grade 4 leucopenia (1 patient) and Grade 3 non-hematologic toxicity, diarrhea (1 patient), dizziness (1 patient) and decreased sodium (1 patient). Treatment administration was delayed for a median of 7 days (range 4–14 days) in 5 patients, mainly for neutropenia (4 patients) and decrease of ALT (1 patient). The reasons for treatment discontinuations were tumor progression (37 patients) and adverse event without recovery

**Table 1** Baseline characteristics and patient demographics

| Characteristic | No. of patients | (%) |
|---|---|---|
| Age (years) | | |
| Median | 65 | |
| Range | 37–79 | |
| Sex | | |
| Male | 33 | 85 |
| Female | 6 | 15 |
| Performance status (ECOG) | | |
| 0 | 30 | 75 |
| 1 | 7 | 20 |
| 2 | 2 | 5 |
| Total no. of cycles | | |
| Median | 3 | |
| Range | 2–8 | |
| Prior therapy | | |
| None | 32 | |
| Surgery only | 3 | |
| Surgery + adjuvant chemotherapy | 4 | |
| Metastatic site | | |
| Abdominal lymph node | 26 | |
| Liver | 23 | |
| Peritoneum | 5 | |
| Cervical lymph node | 5 | |
| Lung | 3 | |
| Histological types of primary tumor | | |
| Intestinal | 21 | 55 |
| Diffuse | 18 | 45 |

within 14 days (2 patients). There were no patients with chemotherapy-related death (Tables 2, 3).

## Efficacy

Tumor response was evaluable according to RECIST in 40 patients. Eighteen patients (45%) achieved a confirmed PR, 11 (27.5%) had stable disease (SD), and 11 (27.5%) progressive disease (PD), as judged by an independent review panel. This resulted, in an ORR of 45% [95% confidence intervals (Cis), 29.4–60.6%]. Median survival time (MST) was

**Table 2** Tumor response

| Characteristic | No. of patients | (%) |
|---|---|---|
| Confirmed response | | |
| Complete response | 0 | 0 |
| Partial response | 17 | 45 |
| Stable disease | 11 | 28 |
| Progressive disease | 11 | 28 |
| 95% CI: 29.4–60.6% | N = 39 | |

**Table 3** Treatment-related adverse events

| Adverse events | Grade 1, 2 No. of patients (%) | Grade 3, 4 No. of patients (%) |
|---|---|---|
| Hematological | | |
| Anemia | 36 (90) | 1 (2.5) |
| Leucopenia | 23 (58) | 4 (10) |
| Neutropenia | 12 (30) | 15 (37.5) |
| Thrombocytopenia | 2 (5) | 0 (0) |
| Non-hematological | | |
| Nausea/Vomiting | 3 (60) | 0 (0) |
| Anorexia | 1 (2.5) | 2 (5) |
| Fatigue | 3 (8) | 1 (2.5) |
| Dizziness | 1 (2.5) | 1 (2.5) |
| Fever | 4 (10) | 0 (0) |
| Alopecia | 39 (100) | |
| Stomatitis | 4 (10) | 0 (0) |
| Diarrhea | 2 (5) | 2 (5) |
| AST↑ | 13 (33) | 0 (0) |
| ALT↑ | 7 (18) | 1 (2.5) |
| Neuropathy | 13 (33) | 0 (0) |
| Hyponatremia | 5 (13) | 2 (2) |
| Duodenal ulcer | | 1 (2.5) |

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase

8.5 months (95% CIs, 8.0–14.9 months, Fig. 1), median TTP was 4.0 months (95% CIs, 2.9–6.2 months, Fig. 2). One- and 2-year OS rates were 35.9 and 14.4%, respectively.

Following completion of this study regimen, a total of 32 (82%) patients received second- and third-line chemotherapies, with 56% receiving CPT-11 (irinotecan) and cisplatin (CDDP) combinations.

## Toxicity

The median number of completed cycles was 3 (range 2–8). The most common treatment-related Grade 3/4 hematological

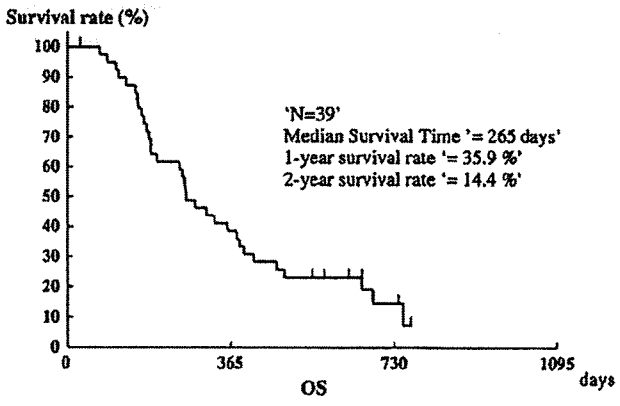


**Fig. 1** Kaplan–Meier curve for overall survival

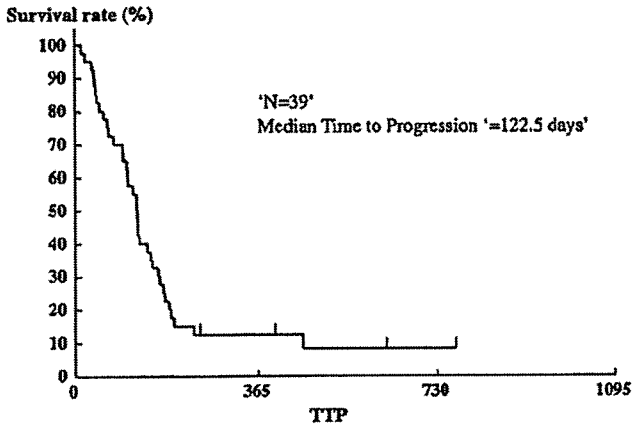


**Fig. 2** Kaplan–Meier curve for time to disease progression. The median time to progression and median overall survival was 122 and 265 days respectively

toxicity was neutropenia (37.5% of patients). All of these patients were successfully treated with granulocyte-colony-stimulating factor (G-CSF) and antibiotics. Grade 3/4 anemia was seen in one patient (2.5%); no Grade 3/4 thrombocytopenia was reported. With non-hematological toxicity, there were very few Grade 3/4 adverse events. Appetite loss, diarrhea, and decreased sodium were each seen in two patients (5%), and dizziness, decrease of ALT, general fatigue and duodenal ulcer were each seen in one patient (2.5%), respectively. The most common Grade 1/2 non-hematological toxicities were alopecia (75% of patients), peripheral neuropathy (32.5%) and elevation of AST (32.5%).

## Discussion

In this current multicenter Phase II study, we have shown that a combination of biweekly paclitaxel and oral S-1, given as first-line chemotherapy for far advanced gastric cancer such as unresectable and recurrent disease has acceptable antitumor activity (in terms of response rate) and a safe toxicity profile. We achieved an ORR of 45%, a median TTP of 123 days, and an MST of 256 days, and we consider these to be clinically meaningful data. We have reported previously the results of Phase I study with this paclitaxel plus S-1 combination regimen, where the response rate was 53% and the MST was 428 days [17]. Mochiki et al. [18] reported on the combination regimen of weekly paclitaxel and S-1 for advanced gastric cancer, and showed a response rate of 54.1% and an MST of over 15.5 months. Moreover, our feasibility study of paclitaxel and S-1 in 52 advanced gastric cancer patients in a single institute reported an MST of 17.0 months (data was not shown). The shorter MST in the current study is possibly due to the inclusion of many patients with very advanced and terminal disease.

Interestingly, we have already reported on 14 cases where we improved long-term survival by giving this regimen after performing radical salvage surgery to reduce the tumor burden [19]. However, unfortunately, there was no case in this current study where a radical operation was associated with clinical CR. Nevertheless, it seems to be a promising regimen to use as a follow-on from salvage gastrectomy in advanced gastric cancer patients.

Compared with some other S-1-based combination regimens, the clinical benefits achieved in this current study were associated with an acceptable and low toxicity profile, as well as good drug compliance. The most common, treatment-related Grade 3/4 hematological toxicity was neutropenia (37.5%), which was manageable and reversible with appropriate treatment with G-CSF and antibiotics. With respect to other hematological and non-hematological toxicities, few led to withdrawal of the patient from the study. Another advantage of this regimen was that patients could receive this combination chemotherapy as outpatients without a restriction on their time for admission; this may depend on the lower percentage of digestive adverse effects such as nausea and anorexia.

It is considered that following-up first-line therapy with second- or third-line combination chemotherapies is important for extending MST and OS. In this study, a CPT-11 plus /CDDP combination was the most popular regimen for second-line chemotherapy. However, we found that there were some cases where the administered dosage was insufficient; both of CPT-11 and CDDP were used with dosage of less than 30 mg/m$^2$ in these cases, and did not reach an effective plasma concentration. Takiuchi et al. [20] have pointed out the importance of second-line chemotherapy in the treatment of gastric cancer. A randomized, controlled trial (RCT), which was conducted as first-line chemotherapy for advanced gastric cancer patients by the Japan Clinical Oncology Group (JCOG 9205), and compared 5-FU alone with 5FU+CDDP, showed that both regimens have almost the same clinical benefit, not only in terms of MST but also in 1- and 2-year survival rates. Seven years later, the JCOG carried out another RCT (JCOG 9912) that compared 5-FU alone versus CPT-11+CDDP versus S-1 alone. In that study, there was no difference in the efficacy results in the three arms. Surprisingly, compared with the earlier JCOG 9205 trial, MST was prolonged by over 4 months in the JCOG 9912 trial. Many new chemotherapeutic agents (e.g., S-1, CPT-11, docetaxel and paclitaxel) were administered in the JCOG 9912 trial, which were not available at the time of the earlier JCOG 9205 study. The improvement in MST may have been linked to these newer, more effective drugs. In the future, it will be important to run clinical trials that investigate the

benefits of second- or third-line regimens as a means of improving the effect of chemotherapy in patients with advanced-stage gastric cancer. We are now running a randomized Phase II trial with a second-line regimen using CPT-11, CDDP and S-1 following a combination of paclitaxel and S-1, as a means of improving the effect of chemotherapy in patients with advanced-stage gastric cancer.

In conclusion, taken together with the results of previous reports of the same regimens, we found that a combination of biweekly paclitaxel and oral S-1 was well tolerated and effective, and propose that it can be considered as another first-line chemotherapy option to patients with advanced gastric cancer.

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INTRODUCTION TO REVIEW ARTICLES

**Junichi Sakamoto**

# Implementation and limitations of meta-analysis of randomized trials from the clinical biostatistician's point of view

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Despite the fact that a meta-analysis (also called an overview) is a conceptually simple process consisting of reanalyzing the data or the results of several independent experiments, its serious implementation in medicine began only at the end of the 1980s. In early breast cancer, significant survival benefits of adjuvant tamoxifen and cytotoxic therapy were established beyond a reasonable doubt, for the first time, by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The first publication from that group included 61 randomized trials among 28 896 patients.[1] Of note, all analyses were based on carefully checked individual patient data. In colorectal cancer, in contrast, a meta-analysis based on summary data from large adjuvant trials of chemotherapy and radiotherapy could not reach a conclusion about the presence or absence of worthwhile survival benefits,[2] and the authors called for further large trials and meta-analyses to be conducted.[3] Encouraged by the success of the EBCTCG in early breast cancer, several meta-analysis groups were established in order to detect or confirm the existence of "moderate but humanly worthwhile" treatment benefits. In early breast cancer, the meta-analysis conducted by the EBCTCG has been continuously updated and its results published every 5 years. The latest publication included 194 clinical trials among 14 5000 women with breast cancer.[4] In colorectal cancer, the Meta-Analysis Group in Cancer (MAGIC) and the Colorectal Cancer Collaborative Group have collected individual patient data since the 1990s, with several important publications for both advanced and curatively resected colorectal cancers.[5,6]

Doubt still prevails among some clinicians about the credibility of the results of meta-analysis. One reason for such skepticism is based on the presumption that a large randomized trial is better than a meta-analysis of many small trials that differ in many respects and which, therefore, cannot be meaningfully combined, even if analyses are stratified by trial. Advocates of large trials claim that only such trials can give conclusive answers to a major clinical question.[7,8] However, these "definitive" trials would typically require several thousand patients, with the corresponding need for massive databases, the maintenance of high-quality data across many centers and often many countries, and therefore huge budgets that are not always available. Several trials looking at related questions may be easier to organize and more cost-effective, leaving a meta-analysis as the best way to combine all the available evidence and draw reliable conclusions about the treatment benefits and harms.

Several large trials for patients with colorectal tumors have recently been implemented in the United States, Europe, and Japan. Nonetheless, most randomized clinical trials performed in the world are still relatively small-sized, with the number of patients rarely exceeding 500, and as such these trials are underpowered and insufficient from a statistical point of view. Do we have to believe the results of such small-sized randomized trials? Probably not, because negative results might result from the inadequate sample size, while positive results would tend to be prominently reported and published sooner than negative results, a phenomenon known as publication bias. Last but not least, some of the trials may be affected by methodological flaws that may or may not be obvious from their published reports. It is unlikely that all trials are subject to similar flaws, which is why the replication of an experiment is such an essential principle in science generally, and in clinical research in particular.

Meta-analyses that are likely to yield reliable answers to important clinical questions should be based on two key principles. First, they should use individual patient data obtained from the principal investigators of all trials included in the meta-analysis.[9] Second, they should use all relevant trials and not just those that happen to be published or are otherwise available.[10–12] Investigators must also be aware of meta-analyses that intentionally eliminate inconvenient data and that may appear respectable, but may lead to seriously misleading results.[13,14]

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A major step towards making the meta-analytic process easier, more transparent, and more reliable, is the statutory clinical trial registration system that was introduced in the United States in 1997. In 2005, the International Council of Medical Journal Editors (ICMJE) adopted a policy requiring that studies be registered in order to be eligible for publication. In the ICMJE policy, a trial must have a prospectively assigned concurrent control or comparison group to trigger the requirement for registration.[15] Clinical trials, whether implemented by a pharmaceutical company, by a group of investigators, or by a single investigator, now have to be equally and prospectively registered in order to be published in quality medical journals. Hence, most if not all trials started after 2005 will be prospectively registered, which will greatly reduce the opportunity for publication bias by making unpublished trials visible (although their results may still take longer to be known).

In this special issue of the *International Journal of Clinical Oncology,* four distinguished expert clinical biostatisticians illustrate the various contributions and roles of meta-analysis; they discuss the implications of subset analyses to yield reliable answers to important clinical questions; and they describe an important initiative recently launched to facilitate future meta-analyses in gastric cancer (GASTRIC, for Global Advanced/Adjuvant Stomach Tumor Research through International Collaboration).[16,17] I hope that these review articles will provide clinicians with a more comprehensive understanding of the meta-analysis of randomized trials, especially of those trials for the treatment of solid tumors of the gastrointestinal tract.

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