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Randomised phase II study comparing dose-escalated weekly paclitaxel vs standard-dose weekly paclitaxel for patients with previously treated advanced gastric cancer

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Background: This randomised phase II trial compared dose-escalated weekly paclitaxel (wPTX) vs standard-dose wPTX for patients with previously treated advanced gastric cancer (AGC).

Methods: Ninety patients were randomised to a standard dose of wPTX (80 mg m⁻²) or an escalated dose of wPTX (80–120 mg m⁻²) to assess the superiority of overall survival (OS) with a one-sided alpha error of 0.3 and a power of 0.8.

Results: The median OS showed a trend towards longer survival in the dose-escalated arm (11.8 vs 9.6 months; hazard ratio (HR), 0.75; one-sided $P=0.12$), although it was statistically not significant. The median progression-free survival (PFS) was significantly longer in the dose-escalated arm (4.3 vs 2.5 months, HR, 0.55; $P=0.017$). Objective response rate was 30.3% with dose escalation and 17.1% with standard dose ($P=0.2$). The frequency of all grades of neutropenia was significantly higher with dose escalation (88.7% vs 60.0%, $P=0.002$); however, no significant difference was observed in the proportion of patients experiencing grade 3 or more (40.9% vs 31.1%, $P=0.34$).

Conclusion: Dose-escalated wPTX in patients with pretreated AGC met our predefined threshold of primary end point, OS ($P<0.3$); however, it did not show a significantly longer OS. Progression-free survival was significantly better with dose escalation.

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In general, the recommended doses of cytotoxic agents are determined in dose-finding studies. However, the sample sizes in dose-finding studies are not large enough to examine individual differences in drug metabolism; therefore, toxicity profiles are likely to be highly variable.¹ In other words, a standard dose may be insufficient to achieve appropriate antitumour effects in patients with faster drug elimination times (Gurney, 2002). This notion is supported by the fact that chemotherapy-induced neutropenia correlates with favourable clinical outcome in several types of cancer (Rankin *et al*, 1992; Poikonen *et al*, 1999; Di Maio *et al*, 2005; Klimm *et al*, 2005; Yamanaka *et al*, 2007; Pallis *et al*, 2008; Kishida *et al*, 2009; Shitara *et al*, 2009, 2010).

Weekly paclitaxel (wPTX) is commonly used for second-line treatment of advanced gastric cancer (AGC) in Japan. A recent randomised phase III study showed that wPTX had nearly similar efficacy when compared with irinotecan as second-line chemotherapy for AGC after failure of first-line chemotherapy using fluoropyrimidines and platinum agents (Hironaka *et al*, 2013). The most common schedule-limiting toxicities of wPTX are neutropenia and cumulative sensory neuropathy (Hironaka *et al*, 2013). We recently studied the significance of neutropenia that occurs during second-line chemotherapy with wPTX (80 mg m⁻²) for AGC (Shitara *et al*, 2010). According to a multivariate Cox model with neutropenia as time-varying covariates, hazard ratios (HRs) of death were 0.61 ($P=0.004$) for patients with mild neutropenia (grades 1–2) and 0.61 ($P=0.009$) for those with severe neutropenia (grades 3–4) (Shitara *et al*, 2010). Our results, in addition to those of other reports that evaluated the correlation between neutropenia and survival (Rankin *et al*, 1992; Poikonen *et al*, 1999; Di Maio *et al*, 2005; Klimm *et al*, 2005; Yamanaka *et al*, 2007; Pallis *et al*, 2008; Kishida *et al*, 2009; Shitara *et al*, 2009), consistently showed that patients experiencing neutropenia during chemotherapy had better outcomes when compared with patients who did not experience neutropenia (Shitara *et al*, 2011). Although dose response effect regarding efficacies and toxicities as well as adequate biomarkers for wPTX are still unknown, these results suggest that neutropenia might be a surrogate marker for adequate antitumour doses of chemotherapeutic agents. However, to the best of our knowledge, no study has prospectively evaluated whether dosing adjustments based on neutropenia could improve the efficacy of chemotherapy. Therefore, this randomised phase II compared dose-escalated wPTX guided by neutropenia *vs* standard-dose wPTX for patients with previously treated AGC.

MATERIALS AND METHODS

Patients. Prior to enrolment in the study, patients must have fulfilled all of the following criteria: (i) presence of histopathologically or cytologically proven unresectable or recurrent gastric adenocarcinoma; (ii) presence of radiographically confirmed or clinically diagnosed disease progression during one or more previous chemotherapy regimens, or recurrence within 6 months after the last adjuvant chemotherapy dose; (iii) Eastern Cooperative Oncology Group performance status (PS) 0–2; (iv) age of 20 years or older; (v) presence of evaluable disease; (vi) adequate bone marrow reserve (leucocyte count ≥ 3000 per mm³, neutrophil count ≥ 1500 per mm³, haemoglobin level ≥ 8.0 g dl⁻¹, platelet count $\geq 100\,000$ per mm³); (vi) adequate hepatic function (aspartate aminotransferase and alanine aminotransferase < 100 IU l⁻¹ (< 200 IU l⁻¹ in patients with liver metastases) and total bilirubin < 1.5 mg dl⁻¹); (vii) adequate renal function (serum creatinine < 2.0 mg dl⁻¹).

Patients are excluded if they met any of the following criteria: (i) previous history of chemotherapy including taxanes; (ii) uncontrollable ascites or pleural effusion; (iii) serious comorbidities. All patients provided written informed consent, and all study

procedures were approved by the appropriate institutional ethics committees in each institution.

Study design and treatment. The aim of this multi-institutional, open-label, randomised phase II study was to evaluate the efficacy of dose-escalated wPTX to determine whether this treatment is promising in comparison with the standard dose of wPTX for the treatment of patients with AGC that has progressed after one or more prior chemotherapy regimens. The study protocol was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (protocol ID UMIN000004055).

In the control arm, wPTX was administered at a starting dose of 80 mg m⁻² intravenously (i.v.) over the course of 1 h weekly on days 1, 8 and 15 for each 4-week period, as reported previously (Hironaka *et al*, 2013). In the experimental arm, wPTX was similarly administered at a starting dose of 80 mg m⁻². Then, if patients did not experience grade 2 or more neutropenia (neutrophil count < 1500 per mm³) or severe toxicity, the dose of wPTX was increased to 100 mg m⁻² on day 8. Similarly, the dose was further escalated to 120 mg m⁻² on day 15 if no toxicity or neutropenia (grade 2 or more) was present. No dose escalation was permitted after day 15. Treatment was resumed on day 29 with the same dose as that of day 15. The treatment was continued with three successive weekly infusions and 1 week of rest for each 4-week period.

Chemotherapy was delayed until recovery from neutrophil count < 1000 per mm³, platelet count $< 50\,000$ /mm³, or any significant persisting nonhaematologic toxicity. For grade 4 neutropenia lasting > 1 week, febrile neutropenia, grade 4 thrombocytopenia, or grade 3 neuropathy or other non-haematologic toxicity, the wPTX dose was reduced by 20 mg m⁻² in both arms. Treatment was discontinued if the tumour progressed, severe toxicity occurred, or if requested by the patient. There was no set maximum number of wPTX administrations. Prophylactic use of granulocyte-colony-stimulating factor (G-CSF) was not permitted, and treatment use of G-CSF was generally recommended in cases of grade 4 neutropenia or febrile neutropenia. The Data Center (Division of Epidemiology and Prevention of Aichi Cancer Center Research Institute) confirmed patient eligibility, and treatment was randomly assigned by 1:1 with minimisation according to stratifying factors for eligible patients. The following three variables were used for stratification: PS (0–1 *vs* 2), measurable lesion (present *vs* absent), and number of previous treatment regimens (1 *vs* 2 or more). Entered patients were randomly assigned to receive a standard dose of wPTX (Arm A) or an escalated dose of wPTX (Arm B).

End points and assessments. The primary end point of this study was overall survival (OS). Overall survival was estimated from the date of study entry to the date of death or last follow-up visit based on Kaplan–Meier product-limit method. Secondary end points included progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and adverse events. Progression-free survival was measured from the date of entry into the trial to the time when progression or death without evidence of progression occurred. Tumour responses were evaluated for all patients every 8 weeks or earlier if there were indications of treatment failure because of toxicity. Objective response rate in patients with measurable disease was calculated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Disease control rate was defined as the proportion of patients who achieved either complete response (CR), partial response (PR), or stable disease (SD) according to RECIST. Adverse events were evaluated with the Common Terminology Criteria for Adverse Events (CTCAEs) version 4.0.

Statistical analysis. The study was designed as a randomised screening phase II trial with a one-sided alpha of 0.3 and a power

of 0.80 for a comparison of OS between the randomised groups, with a possible loss-to-follow-up rate of 20%. One-sided *P* values are presented for primary end point analysis, and two-sided *P* values were used for the remainder of analyses. The full analysis set (FAS) for efficacy analysis was defined as all eligible patients who received at least one dose of wPTX. Patients those who were judged to be ineligible after study registration were excluded from analysis. The assumed median survival time with the standard regimen was 5 months in this heavily pretreated patient population, and the expected survival benefit was 2 months (median survival time of 7 months in the experimental arm). The minimum sample size for each arm was calculated as 42 patients in each arm (total 84 patients), considering a 1-year enrolment period and a minimum follow-up of 1 year. Presuming some patients would be excluded from analysis, a final sample size for each arm was set at 45 patients (90 in total). If expected improvement of OS was demonstrated with dose-escalated wPTX compared with standard dose in this randomised phase II study, dose-escalated arm was regarded as a promising treatment for further phase III study for patients with AGC who failed one or more previous chemotherapy regimens.

Stratified log-rank test was used to compare OS between treatment groups with stratification factors at randomisation. Stratified Cox proportional hazard models were used to calculate HRs and confidence intervals (CIs). Progression-free survival was analysed with the same method as that used for the analysis of OS. Subset analysis of OS and PFS according to each stratifying factors was performed to evaluate the association between treatment effects and prognostic factors. In regards to ORR and DCR, the point estimates and two-sided 95% CIs were calculated and compared using χ^2 test. Frequency of adverse events was also calculated and compared with the χ^2 test for the worst adverse events (all grades and grade 3 or more) observed in each patient during the study treatment.

The Data and Safety Monitoring Committee (DSMC) independently reviewed the report of trial monitor with regards to efficacy and safety. No interim analysis for efficacy was planned.

RESULTS

Patients. From September 2010 to November 2011, a total of 90 patients were enrolled (Figure 1) from 13 institutions. One patient in Arm B did not receive paclitaxel because of tumour bleeding. Therefore, the FAS included 45 patients in Arm A and 44 patients in Arm B. Patients and disease characteristics were well balanced between the two arms (Table 1). Forty-four per cent of patients in arm A and 45% of patients in Arm B received two or more previous lines of chemotherapy. All but one patient received previous fluoropyrimidine, and 78% of patients in arm A and 77% of patients in Arm B received previous platinum agents (mostly cisplatin). Furthermore, 38% of patients in arm A and 41% of patients in arm B received irinotecan prior to this study. All patients discontinued last-line of previous chemotherapy because of progressive disease. The median interval since the initiation of first-line chemotherapy to study entry was 8.6 months (range, 2.1–41.6) in Arm A and 8.3 months (range, 1.3–27.0) in Arm B. The cutoff date for analysis was December 2012, resulting in a median follow-up time of 18 months. Among the 44 patients in the dose-escalated arm, the dose of wPTX was escalated to 100 mg m⁻² in 41 patients (93.2%) and then to 120 mg m⁻² in 29 patients (65.9%). The proportion of patients who had dose reductions during all treatment courses was 20.0% (*N*=9) in Arm A and 31.8% (*N*=14) in Arm B, including those whose doses were escalated and then re-modified. The median number of wPTX administration was 7 (range, 1–39) in Arm A and 11 in Arm B (range, 4–57).

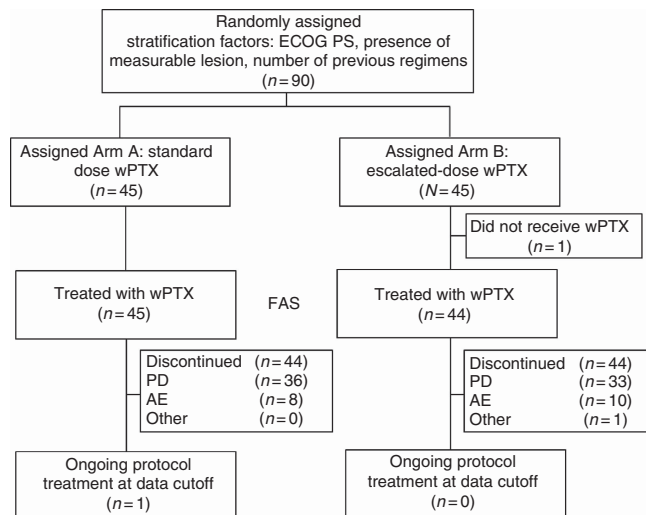


Figure 1. CONSORT flowchart showing the disposition of enrolled patients at the time of data cutoff. Of the 90 patients who were randomly assigned, one patient in the escalated-dose wPTX arm did not receive wPTX because of tumour bleeding. One patient in Arm B discontinued treatment to receive other treatment. Abbreviations: AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set; PD, progressive disease.

The median cumulative dose of wPTX was 536.4 mg m⁻² (range, 80.0–3150.0) in Arm A and 961.7 mg m⁻² (range, 270.0–5680.0) in Arm B. The median wPTX dose per week during all treatment courses was 59.9 mg m⁻² (range, 30.9–80.0) in Arm A and 75.8 mg m⁻² (range, 45.6–107.4) in Arm B. The most common reason for treatment discontinuation was disease progression with 81.8% in Arm A (*N*=36) and 77.2% in Arm B (*N*=34) followed by toxicity (18.2% in Arm A and 22.7% in Arm B, Figure 1).

Efficacy. At the time of analysis, all eligible patients were evaluated for efficacy, and 71 patients (79.8%) had died and no patients were with lost follow-up. The median OS showed a trend towards longer survival in Arm B (11.8 months, 95% CI; 7.6–16.3) with a 2.2-month increment over that in Arm A (9.6 months, 95% CI; 7.4–11.7), although it was statistically not significant (HR, 0.75; 95% CI, 0.45–1.22; one-sided *P*=0.12, Figure 2A). The median PFS was significantly longer in the dose-escalated arm (Arm B, 4.3 months, 95% CI; 3.0–5.7) than in Arm A (median, 2.5 months, 95% CI; 1.8–3.7, HR, 0.55; 95% CI, 0.34–0.90; *P*=0.017, Figure 2B).

Of the 35 patients with measurable lesions in Arm A, six patients achieved PR and 11 patients achieved SD. Meanwhile, among the 33 patients with measurable lesions in Arm B, 10 patients achieved PR and 16 patients achieved SD. The ORR was 17.1% (95% CI; 6.6–33.7) in Arm A and 30.3% (95% CI; 15.6–48.7) in Arm B (*P*=0.2). Disease control rate was significantly higher in Arm B (78.8%; 95% CI, 61.1–91.0) than in Arm A (48.6%; 95% CI, 31.4–66.0; *P*=0.009, Supplementary Table 1). Exploratory analysis by waterfall plot of maximum tumour shrinkage from baseline suggested that significantly higher number of patients in Arm B (22 of 33, 66.7%) achieved a decrease in the best percentage change from baseline when compared with Arm A (13 of 35, 45.5%, *P*=0.014, Figure 3). Subset analysis of OS and PFS indicated that the OS benefit of the dose escalation was more prominent in PS 0–1 patients (*N*=81, median 13.6 in Arm B vs 9.8 months in Arm A, HR 0.69, 95% CI 0.42–1.14, *P*=0.12) than in PS2 patients (interaction *P*=0.01, Figure 4), although the number of PS2 patients is very small (*n*=8). Moreover, patients with measurable lesions showed better results with escalated-dose therapy when compared with patients without measurable lesions, although the

Table 1. Baseline patients characteristics

Characteristics	Arm A (N=45)		Arm B (N=44)	
	N	%	N	%
Age (years)				
Median, range	65	33–80	62	29–78
<65	22	49	25	59
≥65	23	51	19	41
Gender				
Male	29	64	32	73
Female	16	36	12	27
ECOG PS				
0	23	51	22	50
1	18	40	18	41
2	4	9	4	9
Prior gastrectomy				
Yes	20	44	21	48
Adjuvant chemotherapy				
Yes	11	24	16	36
Previous lines of chemotherapy				
1	25	56	24	55
≥2	20	44	20	45
Prior chemotherapy				
Fluoropyrimidine	45	100	43	98
Platinum agent	35	78	34	77
Irinotecan	17	38	18	41
Other	7	16	8	18
Measurable lesions				
Present	35	78	33	75
Metastatic sites				
Lymph node	30	67	28	64
Peritoneum	19	42	21	48
Liver	16	36	13	30
Lung	4	9	4	9
Bone	3	7	4	9
No. of metastatic sites				
1	18	40	15	34
≥2	27	60	29	66

Abbreviation: ECOG PS = Eastern Cooperative Oncology Group performance status.

interaction was not significant (Figure 4). Exploratory analysis of all patients showed better OS in patients who experienced grades 3–4 neutropenia (N=32, median of 15.1 months, HR 0.29, 95% CI, 0.16–0.54) and patients with grades 1–2 neutropenia (N=34, median of 11.2 months, HR 0.44, 95% CI, 0.25–0.78) than patients without neutropenia (N=23, median of 6.4 months, reference, Supplementary Figure 1).

Adverse events. Treatment was well tolerated in both arms. No patients died within 30 days of random assignment. Moreover, no treatment-related deaths were observed. Frequency of neutropenia of all grades was significantly higher in Arm B than that in Arm A

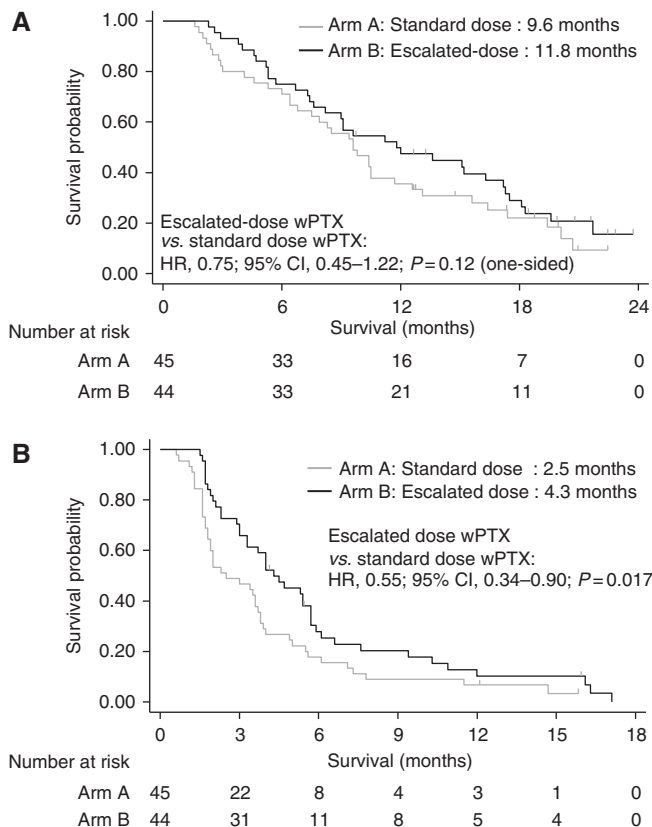


Figure 2. Kaplan–Meier plots of (A) overall survival and (B) progression-free survival in patients treated with a standard dose of wPTX vs escalated-dose wPTX. Abbreviations: CI, confidence interval; HR, hazard ratio.

(88.7% vs 60.0%, P=0.002, Table 2); however, no significant difference was observed in the frequency of grade 3 or 4 neutropenia (40.9% vs 31.1%, P=0.34). Febrile neutropenia was observed in only two patients in Arm A (4.4%) and in one patient in Arm B (2.3%). The frequency of peripheral sensory neuropathy was significantly higher in Arm B than that in Arm A (86.4% vs 62.2%, P=0.009), although the difference in the frequency of grade 3 peripheral sensory neuropathy was not significant when comparing the two groups (13.6% vs 6.7%, P=0.27).

Additional treatments. Additional anticancer treatment was performed in 30 patients (67%) in Arm A and in 35 patients (80%) in Arm B (P=0.23). The most common agent was irinotecan (29% in Arm A and 45% in Arm B). Palliative radiotherapy was performed in seven patients in Arm A (16%) and two patients in Arm B (5%).

DISCUSSION

This study was the first randomised trial to evaluate dose escalation of chemotherapy according to the degree of neutropenia during the early course of treatment for AGC. This study met our predefined threshold of primary end point, OS (P<0.3); however, it did not show a significantly longer OS with dose escalation. Progression-free survival and DCR were better with neutropenia-guided dose-escalated wPTX than with a standard-dose wPTX, which supports the notion that this individualised treatment modification may have the potential to improve wPTX efficacy for patients with pretreated AGC.

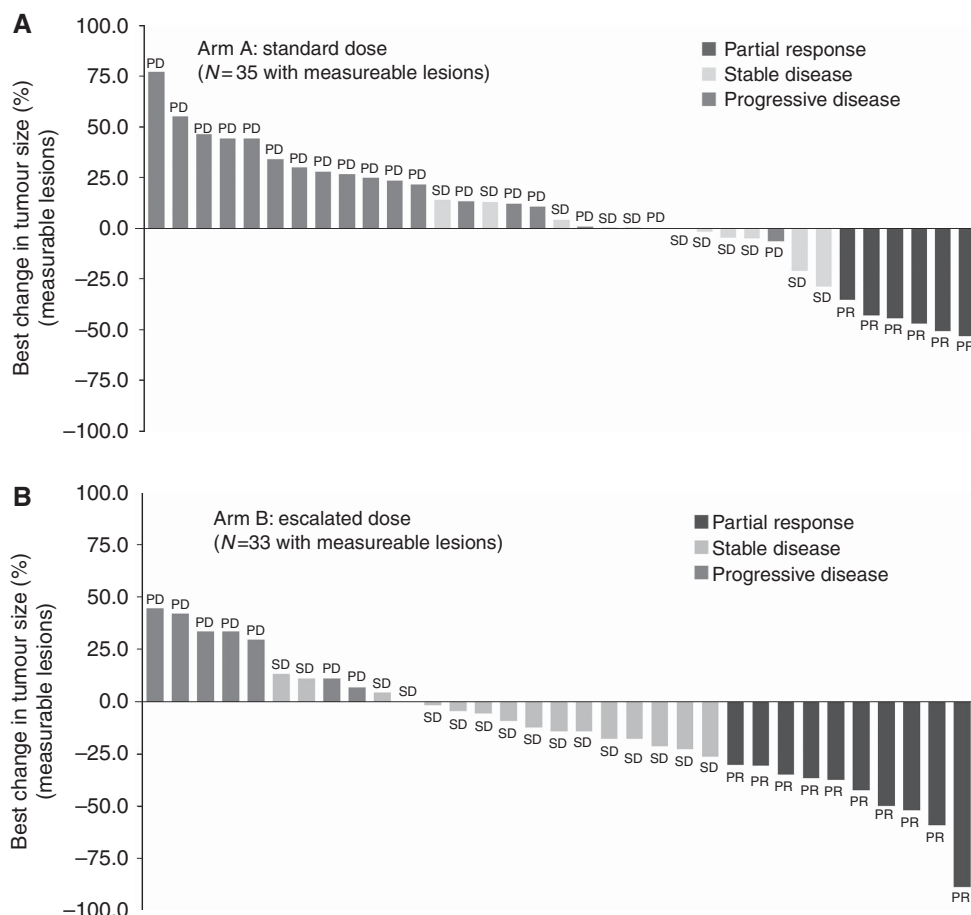


Figure 3. Waterfall plots of best percentage changes in target tumour size in patients receiving a standard dose of wPTX (A) and dose-escalated weekly PTX (B). Significantly higher number of patients in Arm B (22 of 33, 66.7%) achieved a decrease in the best percentage change from baseline when compared with Arm A (13 of 35, 45.5%, $P=0.014$).

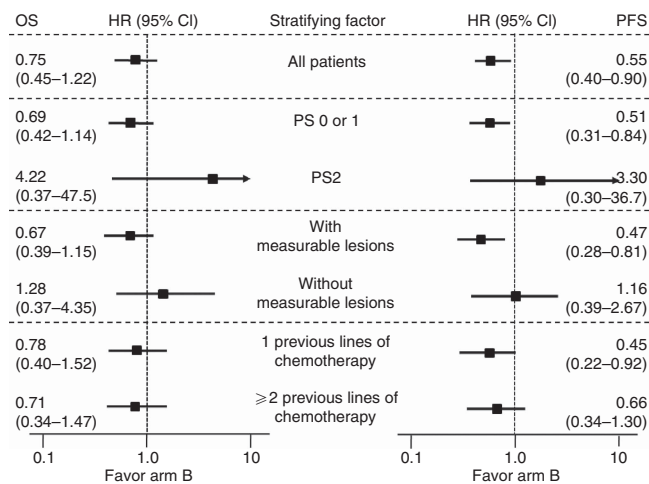


Figure 4. Comparison of overall survival and progression-free survival among patient subgroups treated with a standard dose of weekly paclitaxel (wPTX; arm A) versus escalated-dose wPTX (arm B). Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Several previous randomised studies have evaluated the efficacy of high-dose taxanes when compared with standard-dose taxane for several types of cancers (Harvey *et al*, 2006; Untch *et al*, 2009; Moebus *et al*, 2010; Berry *et al*, 2011; Kim *et al*, 2012). These studies showed controversial results in terms of efficacy, although

toxicities consistently increased when higher chemotherapy doses were used (Harvey *et al*, 2006; Untch *et al*, 2009; Moebus *et al*, 2010; Berry *et al*, 2011; Kim *et al*, 2012). The present study differs from those studies in that the dose was only escalated in stepwise manner for patients who did not experience neutropenia. Our previous retrospective analysis of patients treated with the wPTX therapy for AGC showed that ~80% of patients with neutropenia experienced their highest grade within 4 weeks (Shitara *et al*, 2010). Therefore, we planned to increase the dose early in the treatment course (day 8, day 15). Further, as our previous analysis did not show a significant survival difference between patients with mild neutropenia (grade 1 or 2) and severe neutropenia (grade 3 or 4) (Shitara *et al*, 2010), we set the threshold of the neutrophil count to escalate the dose as $<1.5 \times 10^9$ per l. Following this protocol, the frequency of neutropenia of all grades was significantly higher with dose escalation; however, no significant difference was observed in the frequency of grade 3 or 4 between control arm and dose-escalated arm in this study or other severe toxicities. Further, the proportion of patients who discontinued treatment because of toxicities was almost same when comparing the control arm and the dose-escalated arm. These results suggest that individualised dose escalation of wPTX beyond the standard dose in patients who did not experience neutropenia was well tolerated.

This study showed a statistically significant improvement of PFS with dose escalation; however, the improvement in OS was not statistically significant. There are several possible explanations for this result. First, the OS in both arms were unexpectedly long, despite the fact that previous randomised studies including patients receiving second-line and third-line therapies for AGC

Table 2. Adverse events

Adverse event	Arm A (N=45)				Arm B (N=44)				P-value	
	All grades		Grade 3 or more		All grades		Grade 3 or more		All grades	Grade 3 or more
	N	%	N	%	N	%	N	%		
Leucopenia	33	73.3	10	22.2	39	88.7	10	22.7	0.07	0.95
Neutropenia	27	60.0	14	31.1	39	88.7	18	40.9	0.002	0.34
Anaemia	23	51.1	4	8.9	25	56.8	7	15.9	0.59	0.31
Thrombocytopenia	4	8.9	0	0	1	2.3	0	0	0.18	—
Elevated transaminases	12	26.7	2	4.4	9	20.5	0	0	0.49	0.16
Nausea	7	15.6	0	0.0	10	22.7	0	0.0	0.39	—
Vomiting	2	4.4	0	0.0	3	6.8	0	0.0	0.63	—
Anorexia	15	33.3	3	6.7	15	34.1	2	4.5	0.94	0.66
Diarrhoea	9	20.0	0	0.0	10	22.7	0	0.0	0.75	—
Fatigue	23	51.1	2	4.4	23	52.3	0	0.0	0.91	0.16
Stomatitis	5	11.1	0	0.0	8	18.2	0	0.0	0.35	—
Allergy	0	0.0	0	0.0	3	6.8	0	0.0	0.07	—
Skin toxicity	3	6.7	0	0.0	9	20.5	0	0.0	0.06	—
Peripheral sensory neuropathy	28	62.2	3	6.7	38	86.4	6	13.6	0.009	0.27
Peripheral motor neuropathy	3	6.7	0	0.0	8	18.2	1	2.3	0.099	0.31
Febrile neutropenia	2	4.4	2	4.4	1	2.3	1	2.3	0.57	0.57
Non-neutropenic infection	4	8.9	2	4.4	2	4.5	0	0.0	0.41	0.16
Pneumonitis	1	2.3	0	0.0	1	2.3	0	0.0	0.99	—
Myalgia	8	17.8	0	0.0	8	18.2	0	0.0	0.96	—
Arthralgia	7	15.6	1	2.2	9	20.5	0	0.0	0.55	0.32

reported a median OS of 5–6 months (Shitara *et al*, 2010; Thuss-Patience *et al*, 2011; Kang *et al*, 2012). As only selected patients are eligible to receive second-line or third-line chemotherapy for AGC, selection bias may account for the longer OS seen in the present study. Moreover, post-study treatment may influence OS as shown in a previous phase III study (Hironaka *et al*, 2013). Importantly, dose-escalated treatment did not interfere with the possibility to receive additional chemotherapeutic regimens after treatment. All in all, our observations may suggest that OS is not a desirable end point to use in a randomised phase II setting, although optimal surrogate end points for gastric cancer study is still controversial (Shitara *et al*, 2013). Finally, subset analysis in this study suggested that the efficacy of dose escalation was limited to patients with PS 0–1, although the number of patients with PS 2 is quite small. Performance status 2 patients are rarely included in randomised study of second-line chemotherapy for AGC (Thuss-Patience *et al*, 2011; Kang *et al*, 2012; Hironaka *et al*, 2013), and the benefit of chemotherapy for these patients is unclear (Catalano *et al*, 2008; Wesolowski *et al*, 2009).

This study has several limitations. First, we did not evaluate factors that may contribute to the individual differences in efficacy or toxicity, including neutropenia. Some reports have suggested that several genetic polymorphisms may influence the efficacy or toxicity of PTX treatment (Shitara *et al*, 2010; Leskelä *et al*, 2011; Baldwin *et al*, 2012; Tian *et al*, 2012). Moreover, a previous study of 5-fluorouracil (5-FU) showed that area under the curve (AUC)-directed therapy with individualised doses of 5-FU resulted in improved outcomes (Gamelin *et al*, 2008). Although data regarding genetic polymorphisms or serum drug levels are lacking, the present results still suggest that neutropenia can be used as a marker of chemotherapeutic efficacy for the purposes of dose

escalation, regardless of its mechanisms. Second, the impact of treatment results or toxicities on quality of life (QOL) or symptomatic relief was not evaluated in this study. Longer PFS and higher DCR with dose escalation will hopefully alleviate the tumour-related symptoms of AGC. Therefore, a comprehensive analysis of QOL and tumour-related symptoms should be performed in a subsequent randomised study. Finally, the relatively small sample size of the patient population because of high alpha level in this study represents a major limitation; thus, confirmatory study is necessary.

In conclusion, dose-escalated wPTX in patients with pretreated AGC met our predefined threshold of primary end point, OS ($P < 0.3$); however, it did not show a significantly longer OS. Significantly longer PFS and higher DCR with dose escalation may warrant further investigations in phase III trials, especially for good PS patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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