

Overview



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Title: The Multicenter, Phase II Prospective Study of Paclitaxel Plus Capecitabine as First-Line Chemotherapy in Advanced Gastric Carcinoma

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Disclosures

The authors indicated no financial relationships.

Author Summary: Abstract and Brief Discussion

Background

The efficacy and toxicity of paclitaxel plus capecitabine (PX) as first-line treatment in advanced gastric cancer (AGC) was evaluated.

Methods

Patients with previously untreated AGC were included. PX was given every 3 weeks until a maximum of six cycles or progression. Capecitabine monotherapy was continued for patients without disease progression. The primary endpoint was progression-free survival, and secondary endpoints were objective response rate, overall survival (OS), and safety.

Results

Overall, 194 patients were treated per protocol and one patient was excluded because of allergy to paclitaxel. Response was evaluated in 175 patients, with an objective response rate of 34.8%. After a median follow-up of 33.2 months, disease progression was observed in 141 patients, 137 died, and 16 were lost to follow-up, with progression-free survival of 188 days and OS of 354 days. In multivariate Cox regression analysis, no factor remained an independent predictor of OS. Forty-five patients who received capecitabine monotherapy after PX had longer OS (531 days). Adverse events were mild, and the most common grade 3–4 toxicities were leucopenia and neutropenia.

Conclusion

PX as a first-line treatment has promising efficacy in AGC. Based on these data, a phase III study has been launched for further investigation.

Discussion

Chemotherapy can improve survival and quality of life for patients with AGC. The V325 trial established that docetaxel plus 5-fluorouracil and cisplatin would benefit AGC patients; however, a high rate of hematologic toxicity limits the use of the combination regimen. Paclitaxel has good tolerability and efficacy similar to docetaxel. In addition, paclitaxel has synergistic effects with capecitabine. After approval by the ethics committee, we initiated this multicenter, phase II, prospective trial to evaluate the efficacy and toxicity of PX as first-line treatment in AGC.

Overall, 195 patients were enrolled at 18 centers; 175 patients were evaluable for clinical response. The response rate was 34.8%, and the median overall survival was nearly 1 year (Fig. 1). These efficacy data were similar to docetaxel plus 5-fluorouracil and cisplatin in the V325 trial. Adverse events were well tolerated. The occurrence of grade 3–4 neutropenia decreased to less than 10%. The most common nonhematologic toxicity was alopecia. Although paclitaxel-related neurotoxicity was observed, most cases were mild and reversible under the weekly schedule. No patients discontinued protocol treatment because of paclitaxel-related neuropathy.

In vitro models showed that taxanes can upregulate thymidine phosphorylase activity within 4 days with the maximal effect at about 6–8 days after the treatment. Consequently, a weekly schedule of paclitaxel could provide a synergistic effect in combination with capecitabine. Our results demonstrated that the toxicity of this protocol is generally well tolerated. In our study, there was no modification per protocol for elderly patients, and no severe adverse events occurred during the treatment.

The consensus about the number of palliative chemotherapy cycles that should be performed has not yet been reached. Nevertheless, in clinical practice, tolerability often precludes continuing combination chemotherapy until progression. Furthermore, maintenance chemotherapy has shown benefit in colorectal cancer and lung cancer. We explored maintenance therapy in patients with gastric cancer. In this trial, a subset of 45 patients who continued with the capecitabine monotherapy without disease progression after combination therapy seemed to have obtained longer survival benefit (531 days). Hand-foot syndrome was the main toxicity that restricted the use of capecitabine.

In summary, we can conclude that the efficacy and tolerability of PX observed in our study deserves further investigation in a phase III trial (ClinicalTrials.gov identifier NCT01015339).

Acknowledgements

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Trial Information

Disease:	Gastric cancer
Stage of disease / treatment:	Metastatic / Advanced
Prior Therapy:	None
Type of study - 1:	Phase II
Type of study - 2:	Single Arm
Primary Endpoint:	Progression-Free Survival
Secondary Endpoint:	Overall Response Rate
Secondary Endpoint:	Overall Survival
Additional Details of Endpoints or Study Design:	In this multicenter, open-label, phase II, prospective clinical trial, the primary objective was to evaluate progression-free survival. The secondary objectives included the analysis of response rate, overall survival, and occurrence of adverse events. PFS was calculated from the first day of chemotherapy until the date of progression or date of death, whichever occurred first. The censoring date would be the last date of follow-up or last tumor measurement. Overall survival was calculated from the patient-signed informed consent until death or last date of follow-up. Progression-free survival and overall

survival curves were generated using the Kaplan–Meier method. In univariate analysis, survival rates were compared using the log-rank test. In multivariate analysis, independent prognostic factors were determined by the Cox proportional hazards model. A *p* value of <.05 was considered statistically significant. SPSS version 16.0 was used for all analyses. Tumor response was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST) 1.0. Target lesions were measured by imaging studies (including computed tomography scan and/or magnetic resonance imaging) every two cycles or when there were any clinical signs of possible tumor progression. Tumor responses were confirmed by a second imaging study 4 weeks after initial response. Patients' conditions and treatment-related toxicities were evaluated weekly and were graded using the toxicity criteria of the National Cancer Institute (NCI CTC version 3.0).

Investigator's Analysis: Active and should be pursued further.

Drug Information

Generic/Working name: Paclitaxel

Drug type: Small molecule

Drug class: Tubulin / Microtubules targeting agent

Dose: 80 mg/m²

Route: IV

Schedule of Administration: Days 1 and 8 of a 21-day cycle. Cycles were repeated every 3 weeks until progression or for a maximum six cycles or until occurrence of adverse events or until withdrawal of consent.

Drug 2:

Generic/Working name: Capecitabine

Drug type: Small molecule

Drug class: Antimetabolite

Dose: 1,000 mg/m²

Route: Oral (po)

Schedule of Administration: Day 1 of three 3-week cycles preoperatively and three cycles postoperatively

Drug 3:

Generic/Working name: Capecitabine

Trade name: Xeloda

Company name: Roche

Drug type: Other

Drug class: Antimetabolite

Dose: 1,250 mg/m²

Route: oral (p.o.)

Schedule of Administration: Twice a day on days 1–14 of a 21-day cycle. Cycles were repeated every 3 weeks until progression or for a maximum of six cycles or until occurrence of adverse events (AEs) or until withdrawal of consent. Capecitabine monotherapy (same as the combination stage) was recommended as maintenance therapy until progression or occurrence of unendurable adverse events for patients without disease progression.

Patient Characteristics

Number of patients, male: 127

Number of patients, female: 68

Stage: III or IV

Age:	Median (range): 59 (23–80)
Number of prior systemic therapies:	Median (range): 0 (0)
Performance Status:	ECOG
	0 —
	1 —
	2 —
	3 —
	unknown—
Other:	From December 6, 2006, to April 28, 2010, 195 patients from 18 centers were enrolled in this study. Overall, 194 patients were treated per protocol, and 1 patient was withdrawn from the trial because of allergy to paclitaxel. Median Karnofsky performance status was 80 (range: 70–100).

Cancer Types or Histologic Subtypes

Well-moderately differentiated adenocarcinoma:	52
Poorly differentiated adenocarcinoma:	143

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients screened:	195
Number of patients enrolled:	195
Number of patients evaluable for toxicity:	195
Number of patients evaluated for efficacy:	175
Evaluation method:	RECIST 1.0
Response assessment CR:	1.0%
Response assessment PR:	33.8%
Response assessment SD:	41.0%
Response assessment PD:	13.8%
Response assessment other:	10.3%
(Median) duration assessments PFS	188 days, confidence interval: 150.2–225.8
(Median) duration assessments OS	354 days, confidence interval: 307.7–400.3

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades
	*No Change from Baseline/No Adverse Event						
Leukocytes (total WBC)	44%	23%	17%	11%	3%	0%	55%
Neutrophils/granulocytes (ANC/AGC)	58%	17%	14%	5%	3%	0%	41%
Hemoglobin	85%	10%	3%	1%	0%	0%	14%
Platelets	88%	7%	2%	1%	0%	0%	11%
Hair loss/alopecia (scalp or body)	64%	21%	13%	0%	0%	0%	35%
Fatigue (asthenia, lethargy, malaise)	78%	6%	7%	7%	0%	0%	21%
Nausea	65%	17%	11%	4%	1%	0%	34%
Rash: hand-foot skin reaction	76%	6%	11%	5%	0%	0%	23%
Neuropathy: sensory	83%	4%	8%	4%	0%	0%	16%
Diarrhea	83%	6%	6%	3%	0%	0%	16%
ALT, SGPT (serum glutamic pyruvic transaminase)	86%	7%	3%	2%	1%	0%	13%
Mucositis/stomatitis (clinical exam)	92%	5%	1%	0%	0%	0%	7%
Allergic reaction/hypersensitivity (including drug fever)	99%	0%	0%	0%	0%	0%	0%

Ventricular arrhythmia 98% 0% 0% 1% 0% 0% 1%
*No Change from Baseline/No Adverse Event

Assessment, Analysis, and Discussion

Completion:	Study completed
Pharmacokinetics / Pharmacodynamics:	Not Collected
Investigator's Assessment:	Active and should be pursued further.

Discussion

Although the prognosis of advanced gastric cancer (AGC) patients is very poor, chemotherapy can improve survival and quality of life for these patients [1, 2]. In the V325 trial, docetaxel plus 5-fluorouracil (5-FU) and cisplatin provided a small but statistically significant survival benefit in AGC. A high rate of hematologic toxicity, however, limits the use of this triplet combination regimen [3]. Paclitaxel, the prototype taxane compound that interferes with tubulin assembly, has a similar effect but seemed to be more tolerable than docetaxel in a phase II study when combined with 5-FU as first-line chemotherapy in patients with AGC [4]. Capecitabine is an oral fluoropyrimidine with good tolerability, designed to deliver 5-FU selectively to tumor tissues via thymidine phosphorylase metabolism [5–7]. From the meta-analysis of the ML17032 and REAL2 trials, patients with gastric cancer could benefit more from capecitabine than from 5-FU [8]. Paclitaxel and capecitabine (PX) have synergistic effects because paclitaxel can upregulate TP to increase the intratumor concentration of 5-FU [9]. In addition, their toxicity profiles are different. Consequently, we have initiated a multicenter, phase II, prospective clinical trial to evaluate the efficacy and safety of PX as first-line treatment for AGC.

The results of our study show that PX has good efficacy as first-line chemotherapy in AGC. For the intent-to-treat population, the response rate observed in our study was 34.8%, and overall survival (OS) was nearly 1 year (Fig. 1). These efficacy data were similar to docetaxel plus 5-FU and cisplatin in the V325 trial. In addition, this efficacy was also comparable with titanium silicate 1 plus cisplatin in a controlled phase III trial by Jin et al. [10]. In the subgroup of patients who obtained clinical benefits (complete response plus partial response plus stable disease), the median OS was statistically longer than those with no clinical benefit from this regimen. (392.0 days vs. 219 days, $p = .000$; Fig. 2). After chemotherapy, 15 patients with initially inoperable advanced disease underwent radical resection. There were no serious perioperative complications; the patients recovered well from surgery and had much longer survival (data not shown). In our study, we could not distinguish which group of patients could benefit more from this regimen; therefore, translational research to explore the pharmacogenetic status of these patients might prove useful in further stratification of patients.

In contrast, the toxicities observed in our study were lower than those observed in other doublet regimens and clearly improved when compared with the triplet regimen. The occurrence of grade 3–4 neutropenia decreased to less than 10%. The most common nonhematologic toxicity in our study was alopecia. Although paclitaxel-related neurotoxicity was observed, most cases were mild and reversible under the weekly schedule. No patients discontinued protocol treatment because of paclitaxel-related neuropathy. In vitro models have shown that taxanes can upregulate thymidine phosphorylase activity within 4 days, with the maximal effect at about 6–8 days after the treatment [9]. Consequently, a weekly schedule of paclitaxel could provide a synergistic effect in combination therapy with capecitabine. Our results demonstrated that the toxicity of this protocol is generally well tolerated. In our study, there was no modification per protocol for patients older than 65 years. These patients had good tolerance, and no severe adverse events occurred during the treatment. Because the incidence of gastric cancer is steadily increasing among elderly patients, PX could be a treatment option for this subpopulation of patients with gastric cancer.

Consensus about the number of palliative chemotherapy cycles that should be performed has not yet been reached. The majority of oncologists prefer to give chemotherapy until progression or intolerance to maintain response. Nevertheless, in clinical practice, it is difficult to continue combination chemotherapy with good tolerance until disease progression. Consequently, it is vital to prolong progression-free survival with good tolerance. Maintenance chemotherapy has shown more benefit in colorectal cancer [11] and lung cancer [12]. Gastric cancer patients diagnosed at an advanced stage generally have poor physiological status, and there is no convincing evidence to show the benefit of maintenance therapy in AGC; therefore, it seems worthwhile to explore this treatment model in gastric cancer patients. In this trial, 45 patients who continued with capecitabine monotherapy with clinical benefit (complete response plus partial response plus stable disease) after combination therapy seemed to obtain a longer survival benefit. Hand-foot syndrome was the main toxicity effect that restricted the use of capecitabine.

The incidence of proximal gastric cancer is increasing and usually has a poorer prognosis than gastric cancer with distal localization. In addition, retrospective analysis suggested that patients with proximal gastric adenocarcinoma would benefit more from chemotherapy [13, 14]. Although the design of our study did not include as a primary objective the efficacy testing of PX in relation to primary tumor localization, we collected the data for primary tumors according to the Japanese Classification of Gastric Carcinoma [15] to do further analysis. We found that patients with proximal gastric tumors seemed to obtain longer progression-free survival (259 days vs. 168 days, $p = .053$) than patients with distal tumors, but no difference in OS was observed.

In conclusion, our study was a large-sample, multicenter, phase II clinical trial that aimed to explore the efficacy and safety of PX in the first-line treatment of AGC. Our findings suggest that this regimen has good efficacy and tolerance and thus could be a choice for chemotherapy-naïve gastric cancer patients. Based on the preliminary data of this study, a phase III study has been launched for further investigation (ClinicalTrials.gov identifier NCT01015339).

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Figures and Tables

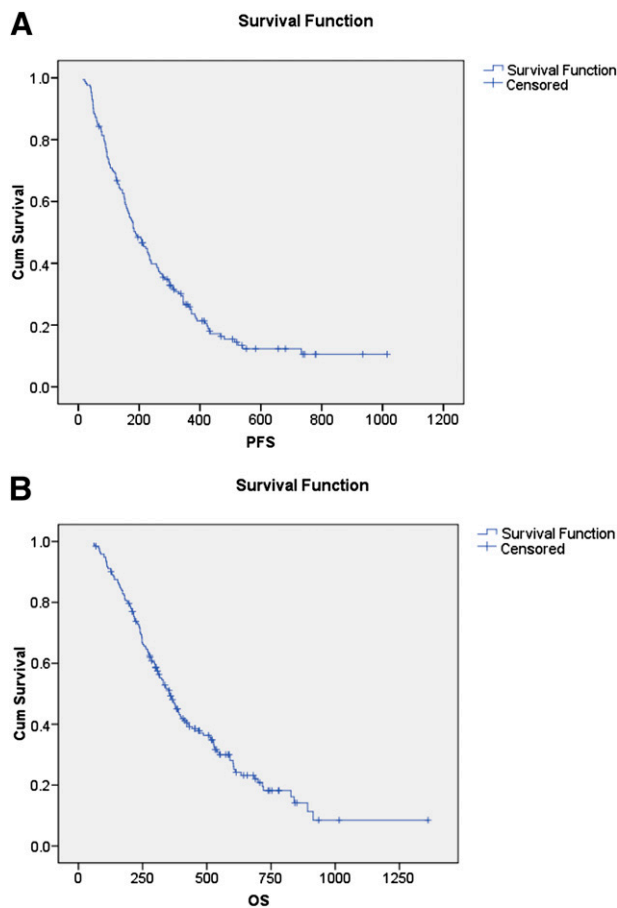


Figure 1. Kaplan-Meier-estimated PFS (A) and OS (B), in days, in all patients.
Abbreviations: Cum, cumulative; OS, overall survival; PFS, progression-free survival.

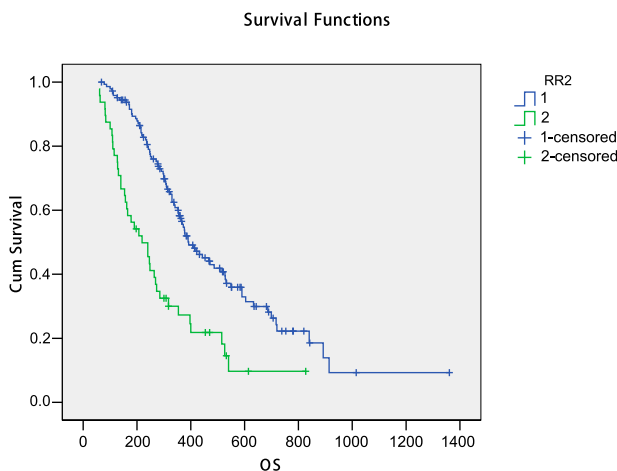


Figure 2. Patients with clinical benefit (complete response or partial response or stable disease) obtained longer OS than those without a clinical benefit (392.0 days vs. 219 days, $p = .000$).
Abbreviations: Cum, cumulative; OS, overall survival; RR2, second response rate.

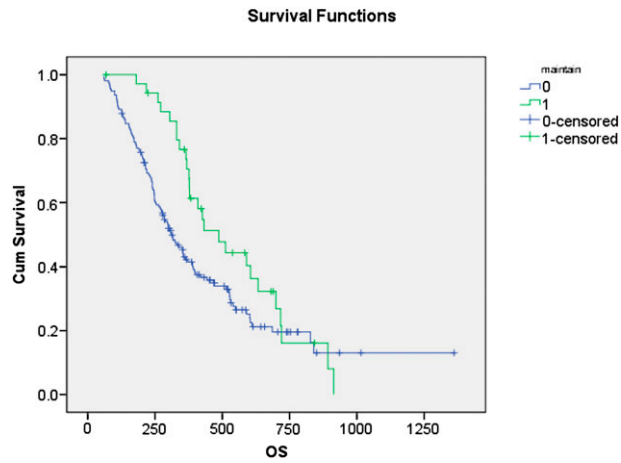
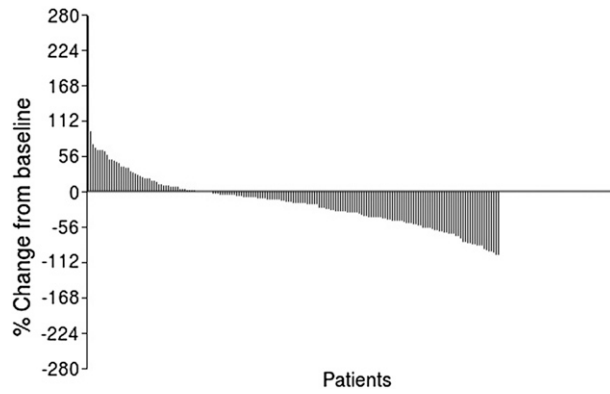


Figure 3. A total of 45 patients completed the combination treatment without disease progression and then entered a capecitabine monotherapy stage. These patients seemed to have longer median OS than the group with CR/PR/SD (531 days vs. 392 days, $p=0.26$).



Waterfall Plot. Waterfall plot of the overall response measured by RECIST 1.0.

Table 1. Patients' characteristics (*n* = 195)

Patient characteristics	Median	%
Age, years, median (range)	59 (23–80)	
Sex		
Male	127	65.1
Female	68	34.9
Eastern Cooperative Oncology Group performance status		
0	43	22.1
1	113	57.9
2	39	20.0
Disease location		
Distal part	138	71.8
Proximal part	57	29.2
Histology		
Well or moderately differentiated	52	26.7
Poorly differentiated (signet ring cell, mucinous, undetermined)	143	73.3
Extent of disease		
Locally advanced	52	26.7
Metastatic	143	73.3
Metastatic sites		
1	57	39.9
2	61	42.7
>2	25	17.5
Prior adjuvant chemotherapy		
No	144	73.8
Yes	51	26.2

Table 2. Toxicity possibly, probably, or definitely attributable to chemotherapy (*n* = 195)

Adverse events	Grade 1–2 Toxicities		Grade 3–4 Toxicities	
	No. of patients	%	No. of patients	%
Hematological				
Leucopenia	81	41.5	28	14.4
Neutropenia	64	32.8	17	8.8
Anemia	27	13.8	2	1.0
Thrombocytopenia	19	9.7	3	1.5
Nonhematological				
Alopecia	42	21.5	27	13.8
Fatigue	27	13.8	14	7.2
Nausea/vomiting	57	29.2	11	5.1
Hand-food syndrome	35	17.9	11	5.1
Neurotoxicity	24	12.3	8	4.1
Diarrhea	26	13.3	7	3.6
Hepatic dysfunction	21	10.8	6	3.1
Stomatitis	13	6.7	1	0.5

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