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ORIGINAL ARTICLE

A phase II trial of weekly fractionated irinotecan and cisplatin for advanced gastric cancer

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Abstract
Purpose This study was to evaluate the activity and the safety of a combination chemotherapy regimen of weekly fractionated irinotecan and cisplatin in advanced gastric cancer patients.
Methods Patients with advanced gastric adenocarcinoma with either chemotherapy-naive or only one prior chemotherapy regimen received irinotecan 50 mg/m^2 followed by cisplatin 30 mg/m^2. Both drugs were administered weekly for 3 consecutive weeks, followed by 1-week rest. Treatment was repeated until disease progression occurred. Response evaluation was performed according to the RECIST criteria.
Results Forty-seven patients (13 chemo-naive, 34 prior chemotherapy) were enrolled. Of 46 evaluable patients, overall response rate was 25.5% (95% CI, 12.9–39.3%) and disease control rate was 63.8% (95% CI, 50.9–79.5%) by intent-to-treat analysis. The time to progression and overall survival duration were 21 and 44 weeks, respectively. One-year survival rate was 41.6%. The most frequent grade 4 toxicity was neutropenia, which was the major cause of treatment delay. Non-hematological toxicities of grade 3–4 were rare with occurrence rate of 14.9% for anorexia and emesis.
Conclusions Fractionated irinotecan combined with cisplatin with 3-week-on and 1-week-off schedule produced favorable clinical results for advanced gastric cancer. Because of the feasible efficacy and low non-hematologic toxicity, this treatment could be a promising salvage regimen in patients who have failed to taxanes.

Keywords Gastric neoplasms · Weekly fractionation · Irinotecan · Cisplatin · Phase II

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Introduction

Gastric cancer is a leading cause of cancer death worldwide and the prolongation of patients' survival remains a challenge for oncologists. Since randomized trials showed that combination chemotherapy improves both quality of life and survival compared with best supportive care, various regimens has been exploited [5, 13].

Combination of 5-FU with doxorubicin, methotrexate, etoposide, or cisplatin has been widely examined in an attempt to achieve better efficacy and survival benefit. European trials have investigated combination regimens of ECF (epirubicin-cisplatin-5-FU) and PELF (cisplatin-epirubicin-5-FU-leucovorin). These regimens showed better tumor response when compared to older regimens such as FAM (5-FU-doxorubicin-mitomycin-C) and FAMTX (5-FU-doxorubicin-methotrexate). However, these regimens accompanied substantial toxicities, and increased tumor response

has not led to satisfactory survival prolongation [3, 4, 24, 25]. This prompted to develop more active and comfortable regimens.

Cisplatin shows a response rate of 30% in gastric cancer [15], and from the findings that cisplatin-containing regimens have demonstrated a higher efficacy than non-cisplatin-containing regimens, cisplatin has been a mainstay component of combination chemotherapy in gastric cancer [11, 23]. Irinotecan has been actively included in the gastric cancer treatment as a novel agent, and 18% response rate with monotherapy has been reported in phase II studies, regardless of prior chemotherapy [9]. The in vitro synergism, lack of cross-resistance, different mechanisms of action, and different toxicity profiles of irinotecan and cisplatin prompted several prospective studies, which confirmed the feasibility and activity of this combination. In Japan, this combination has been investigated mostly according to the schedule of biweekly irinotecan and monthly cisplatin [2]. On the contrary, US groups have tried the 4-week-on and 2-week-off schedules inspired by the report of Saltz et al. [1, 19]. The response rate was equally promising (52–59%); however, adverse effects—especially non-hematologic toxicity including diarrhea and fatigue—were severe and problematic with both schedules. Given these results, the dosage and schedule of irinotecan and cisplatin combination have been pointed out and reconsidered [20]. Herein, we conducted a phase II study using a fractionated schedule of 3 weeks of treatment with cisplatin and irinotecan combination followed by 1-week rest to determine its activity and safety in advanced gastric cancer patients.

Materials and methods

Patient eligibility

The eligibility criteria for the protocol were as follows: (1) histologically documented gastric cancer with metastatic disease; (2) Eastern Cooperative Oncology Group (ECOG) performance scale 0–2; (3) either chemotherapy-naive or only one prior chemotherapy regimen completed 3 weeks before entry; (4) at least one lesion of longest diameter > 10 mm as measured by spiral computed tomography (CT); (5) age ≥ 18 years old; (6) life expectancy ≥ 3 months; (7) adequate bone marrow, hepatic, and renal function (neutrophil ≥ 1,500/μl, platelets ≥ 100,000/μl, serum creatinine ≤ 1.5 mg/dl, total bilirubin within upper limit of normal (ULN), and serum transaminase ≤ 2.5 × the ULN); and (8) no other active malignancies. Patients were excluded from the study if they had concurrent cancer, peripheral neuropathy of the National Cancer Institute common toxicity criteria (NCI-CTC) grade ≥ 2, brain metastasis, prior use of cisplatin or irinotean, or uncontrolled significant comorbid conditions. The study was approved by the Institutional Review Board, and informed consent was obtained from all of the patients before they entered the study.

Treatment plan

Chemotherapy was administered in an outpatient clinic. A starting dose of rinotecan 50 mg/m^2 was given intravenously for 60 min, followed by cisplatin 30 mg/m^2 which was infused for 90 min following 1-h interval. Both drugs were administered weekly for 3 consecutive weeks (D1, D8, and D15), followed by 1 week of rest, defining a 4-week treatment cycle.

All patients received adequate hydration before and after receiving cisplatin. Patients were premedicated with intravenous ondansetron and dexamethasone and also received proper oral medication to reduce diarrhea and delayed emesis. In the case of hematologic toxicity, the next cycle was delayed weekly until neutrophil count > 1,500/μl and platelet count > 100,000/μl were achieved. Granulocyte-colony stimulating factor (G-CSF) was used if patients developed grade 4 neutropenia. G-CSF was not planned as a prophylactic aim. Neither dose reduction nor dose escalation of chemotherapy was allowed. Chemotherapy was given until disease progression, unacceptable toxicity occurred, or treatment withdrawal by the patient.

Patient evaluation

Baseline evaluations of each patient included a complete medical history, physical examination, complete blood count (CBC) with differential, serum chemistries with electrolytes, tumor markers, urine analysis, and electrocardiography. Computed tomography (CT) scans of the measurable lesions were performed at least 4 weeks prior to the initiation of treatment. Fiberoptic gastroduodenoscopy was planned for the patients with a complete remission (CR) of all measurable lesions.

During treatment, patients were evaluated by weekly CBC with differential. A physical examination, performance status, tumor markers, and serum chemistries were evaluated prior to each subsequent cycle. Imaging studies for the measurable lesions were repeated every two cycles.

Treatment response was evaluated according to the guidelines of the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. Patients were

considered assessable for response if they had clinical evidence of early disease progression or if they had received a minimum of two cycles of treatment with at least one tumor measurement. Patients were considered as assessable for response if they had evidence of early disease progression clinically or radiologically within 2 cycles, or if they had received minimal 2 cycles of treatment with at least one tumor measurement. Measurable lesion was defined as $\geq$ 10 mm in any one dimension assessed by spiral CT scan. Evaluable lesion was defined as any other lesions except those with measurable disease. If a patient was documented as having a CR or a partial response (PR), a confirmatory was performed at least 4 weeks after the first radiographically evident tumor response. Time to progression (TTP) was defined from the start of the treatment until disease progression occurred, and overall survival (OS) was calculated from the starting day to death. Time to response was defined as the time between initiation of therapy and a documented response (PR or CR), and response duration was defined from the initial response until progression of disease.

We compared the changes in tumor markers (CEA and CA19-9) with the radiological tumor response [26]. A biological PR was defined as a decrease of tumor marker over 50%. A biological progressive disease (PD) was defined as its increase over 25%. Other changes not satisfying the above criteria were designated as biological stable disease (SD).

All the patients were evaluated for toxicity from the time of their first treatment cycle. Toxicity was evaluated weekly and recorded as a grade according to the NCI-CTC (Version 2.0) for each patient.

Statistical analysis

Analysis was performed using the SPSS 10.0 program (SPSS, Chicago, IL, USA). Time-dependent variables were estimated with a Log rank test using the Kaplan–Meier method. Multivariate analysis was performed using Cox's proportional hazard regression model.

The regimen was planned for both chemotherapy-naive and chemotherapy-exposed patients, and we thus hypothesized the treatment regimen as active if the response rate exceeded 20%. The hypothesis was that H0: $P < P_0$ (0.05) versus H1: $P > P_1$ (0.20) with $\alpha = 0.05$, and $\beta = 0.10$ (90% power). The number of patients required for the study was determined according to a Simon's optimal design [22]. Forty-one patients who met the criteria for the tumor response evaluation were required in order to achieve the desired statistical power. Taking into considering a 10% dropout rate, the required minimum number of enrolled patients was determined to be 46.

Results

Patient characteristics

From January 2003 to May 2004, a total of 47 patients were enrolled, and 46 patients were evaluable for tumor response. One patient was excluded from the response evaluation because he refused to be involved in the study after the first cycle of chemotherapy by himself. Patient characteristics are summarized in Table 1. Of the enrolled patients, 29 (61.7%) were men, and the median age was 55 years (range, 27–69 years). Twenty-two patients had received prior gastrectomy. Thirty-four patients received prior chemotherapy of one regimen. The median cycle number of previous chemotherapy was 6 (range 2–10) with a median dose intensity of 0.86. The overall response rate and disease control rate of previous chemotherapy of the 34 patients were 32.3

Table 1 Patient characteristics

Number of enrolled patients		47
Number of evaluable patients		46
Sex, *n* (%)	Male	29 (61.7)
	Female	18 (38.3)
Age	Median (range)	55 (27–69)
ECOG, *n* (%)	0–1	28 (69.5)
	2	19 (30.5)
Previous chemotherapy, *n* (%)	No	13 (27.7)
	Yes	34 (72.3)
	5-FU + leucovorin + docetaxel	26 (76.5)[a]
	5-FU + leucovorin + paclitaxel	6 (17.6)[a]
	5-FU + doxorubicin + mitomycin-C	2 (5.9)[a]
Histology, *n* (%)	Well to moderately differentiated	11 (23.4)
	Poorly differentiated	23 (48.9)
	Signet ring cell	10 (21.3)
	Mucinous	2 (4.3)
	Hepatoid	1 (2.1)
Previous operation, *n* (%)	No operation	18 (38.3)
	Total gastrectomy	12 (25.5)
	Subtotal gastrectomy	10 (21.3)
	Open and closure	7 (14.9)
Median cycle of previous chemotherapy (range)	6 (2–10)	
Median RDI of previous chemotherapy (range)	0.86 (0.52–1.00)	

ECOG Eastern Cooperative Oncology Group

[a] In a total of 34 patients

and 70.6%, respectively. All these patients had received infusional 5-FU as a component of combination chemotherapy, and the most commonly adopted regimen was docetaxel combined with 5-FU and leucovorin.

All but nine patients had more than one metastatic lesion. The median number of metastatic sites per patient was 2 (range, 1–5), and the main metastatic sites included liver ($n = 26$), abdominal lymph node ($n = 18$), and abdominal mass ($n = 16$). The most common non-measurable lesion was a primary gastric mass ($n = 21$), and ten patients had peritoneal carcinomatosis documented by CT scan. The median initial values of CEA and CA 19-9 was 2.8 ng/ml (range, 0.2–158 ng/ml) and 18.8 U/ml (range, 0–4,760 U/ml), respectively.

Treatment and dose intensity

Total of 206 cycles were administered, corresponding to 824 weeks, with a median of 4 cycles (range, 1–9). Two hundred and eighteen weeks (26.4%) were delayed, and the median delay in weeks per cycle was 0.8 (range, 0–4.3). Eighty-one weeks were intercyclic delay, and 137 weeks were intracyclic delay. The median dose intensity of cisplatin was 18.9 mg/m^2/week (range, 9.3–22.5) and that of irinotecan was 31.4 mg/m^2/week (range, 16.3–37.5). The average relative dose intensity of the regimen was 0.84 (range, 0.41–1.00).

Efficacy

The overall objective response rates are summarized in Table 2. Of the 46 evaluable patients, 3 achieved a CR, 9 a PR, and 18 patients had SD. The overall response rate was 25.5% (95% CI, 12.9–39.3%) and the disease control rate was 63.8% (95% CI, 50.9–79.5%) by intent-to-treat analysis. The median time to response was 10 weeks (range, 6–26), and the median response duration was 27 weeks (range, 8–44). Of the 12 patients that responded, 8 responses were documented after two cycles of chemotherapy. When the response rate was analyzed according to the metastatic sites, abdominal lymph nodes showed a relatively better response compared to the other metastatic lesions (50.0 vs. 28.8%) (Table 3).

The response rate was evaluated post hoc according to the prior exposure to chemotherapy. Among 13 chemotherapy-naive patients, one patient dropped out before completing his second cycle. Of the 12 remaining patients in this subgroup, 2 patients showed a CR and 3 achieved a PR. The overall response rate was 38.3%. Five patients had SD and the resulting disease control rate was as high as 76.8%. The median time to response in this group was 8 weeks, and the median response duration was 32 weeks. Among the 34 patients with a history of prior chemotherapy (including adjuvant chemotherapy), 1 patient had a CR, and 6 achieved a PR, resulting in an overall response rate of 20.5%. The median time to response was 11 weeks and the median duration of response was 20 weeks.

Twenty-five patients (53.2%) (8 from chemotherapy-naive group, 17 from prior chemotherapy group) were switched over to a salvage regimen after disease progression occurred, among whom seven patients (28%) showed an objective response to the next regimen. The concordance rate between tumor response and tumor markers was only 41.3% for CEA, 54.3% for CA 19-9, and 53.2% for either, suggesting that these tumor markers at least were not good indicators of chemotherapeutic response with this regimen.

Table 2 Response evaluation

	Total			Chemotherapy-naive			Prior chemotherapy		
Number of total patients	47			13			34		
Number of evaluable patients	46			12			34		
	N	ITT (%)	PP (%)	*N*	ITT (%)	PP (%)	*N*	ITT (%)	PP (%)
Complete response	3	6.4	6.5	2	15.3	16.7	1	2.9	2.9
Partial response	9	19.1	19.6	3	23.0	25.0	6	17.6	17.6
Stable disease	18	38.4	39.1	5	38.5	41.7	13	38.2	28.2
Progressive disease	16	34.0	34.8	2	15.3	16.7	14	41.1	41.1
Response rate		25.5	26.1		38.3	41.7		20.5	20.5
Disease-control rate		63.8	65.2		76.8	83.4		58.7	58.7

N number, *ITT* intent-to-treat analysis, *PP* per protocol analysis

Survival

With a median follow-up duration of 84 weeks (range, 25–133), 40 patients had disease progression and 29 of them (61.7%) died. The most common site of progression was peritoneal seeding (32.1%), followed by liver (20.1%), and intraabdominal lymph node(s) (14.3%). The median TTP for the overall evaluable patients was 21 weeks (95% CI, 16–26) (Fig. 1), 29 weeks (95% CI, 16–42) for the chemotherapy-naive patients, and

Table 3 Response evaluation by metastasis sites

Organ	Number of measurable lesion	Complete response	Partial response	Stable disease	Progressive disease	Not evaluable	RR (%)	DCR (%)
Liver	26	4	4	9	9	–	30.7	65.4
Abdominal mass	16	3	1	5	5	2	25.0	56.3
Abdominal LN	18	3	6	5	4	–	50.0	77.8
Cervical LN	4	1	0	2	1	–	25.0	75.0
Others	13	1	3	4	5	–	30.8	61.5
Total	77	12	14	25	24	2	33.8	66.2

LN lymph node, *RR* response rate, *DCR* disease-control rate

19 weeks (95% CI, 15–23) for the patients with prior chemotherapy.

The median OS for all patients was 44 weeks (95% CI, 31–57) (Fig. 1); 39 weeks (95% CI, 29–49 weeks) for the patients with prior chemotherapy while the median value has not yet been reached for the chemotherapy-naive patients. One-year survival rate of all the patients was 41.6%; those for chemotherapy-naive and prior chemotherapy were 60.5 and 31.0%, respectively.

When we compared the survival profile according to clinical parameters by multivariate analysis, previous exposure to chemotherapy ($P = 0.012$), well-moderate histology ($P = 0.038$), low initial CA 19-9 ($P = 0.009$), and relatively high-dose intensity ($P = 0.029$) were found to be significant for progression-free survival (PFS). For OS, only moderate significance ($P = 0.17$) was noticed with prior exposure to chemotherapy.

Toxicity

The toxicity profile is summarized in Table 4. The most common grade 3 and 4 hematological toxicity was neutropenia, which was found in 23.4 and 10.6% of patients, respectively. Leukopenia and anemia of grade 3 were also observed in 19.1% of the patients, respectively. Twenty-three patients required G-CSF support before the completion of the second cycle. The average frequency of G-CSF administration of all the patients was one single dose per cycle (range, 0–7). Thirty-three patients received a transfusion of at least one unit of fresh packed RBC. The median unit of RBC transfused was two packs, which corresponds to 0.5 U per cycle. Febrile neutropenia was documented in only three patients (6.4%), and was completely resolved with supportive care. Grade 3–4 thrombocytopenia was documented in 15.2% of patients without bleeding complications. There was no case of treatment-related mortality.

The most common grade 3 non-hematological toxicities were anorexia, nausea, and vomiting. Grade 3 diarrhea was observed in only two patients (4.3%). Grade 3 peripheral neuropathy was observed in one patient. There was one case of grade 3 infection during chemotherapy—lung abscess—and it was recovered completely with supportive care.

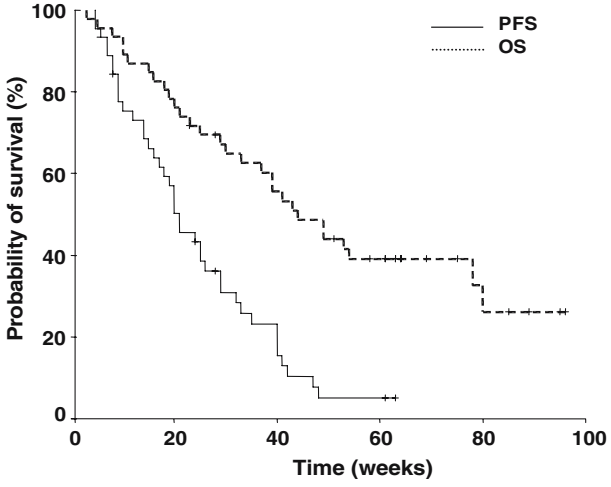

Fig. 1 Survival curves of all patients

Discussion

Gastric cancer is considered as a moderately chemosensitive disease. In unresectable advanced gastric cancer, systemic chemotherapy has been accepted as a palliative treatment for improvement of survival and of quality of life compared to the best supportive care [7, 13]. Although different combination regimens have shown wide-ranging response rate of 25–70%, no regimen has consistently demonstrated clinically relevant improvement over the others. Therefore, a standard regimen has not yet been established, and all the efforts toward developing an effective regimen using novel agents focus on improving survival with less toxicity.

In vitro analyses have revealed a synergistic antitumor activity of irinotecan and cisplatin [10, 12, 14]. The mechanism of synergy comes from the inhibitory effect

Table 4 Toxicity profiles per patient according to NCI-CTC grade

	No of patients[a] (%)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicity					
Anemia	6 (12.8)	9 (19.1)	23 (48.9)	9 (19.1)	–
Leukopenia	10 (21.3)	8 (17.0)	20 (42.5)	9 (19.1)	–
Neutropenia	11 (23.4)	12 (25.5)	8 (17.0)	11 (23.4)	5 (10.6)
Thrombocytopenia	26 (55.3)	9 (19.1)	7 (14.9)	3 (6.4)	2 (4.3)
Non-hematologic toxicity					
Diarrhea	18 (38.3)	19 (40.4)	8 (17.0)	2 (4.3)	–
Anorexia	12 (25.5)	19 (40.4)	9 (19.1)	7 (14.9)	–
Nausea	8 (17.0)	13 (27.6)	19 (40.4)	7 (14.9)	–
Vomiting	17 (36.2)	12 (25.5)	11 (23.4)	7 (14.9)	–
Mucositis	32 (68.1)	11 (23.4)	3 (6.4)	1 (2.1)	–
Peripheral neuropathy	32 (67.4)	8 (17.0)	6 (12.8)	1 (2.1)	–
Constipation	44 (93.6)	2 (4.3)	1 (2.1)	–	–
Skin rash	41 (87.2)	3 (6.4)	3 (6.4)	–	–
Pain	14 (29.8)	21 (44.7)	11 (23.4)	1 (2.1)	–
Elevated creatinine	37 (78.7)	9 (19.1)	1 (2.1)	–	–
Elevated aminotransferase	30 (63.8)	13 (27.6)	3 (6.4)	1 (2.1)	–
Hyperbilirubinemia	38 (80.8)	8 (17.0)	1 (2.1)	–	–

NCI-CTC National Cancer Institute Common Toxicity Criteria

[a] In a total of 47 patients

of SN-38, active metabolite of irinotecan, on the removal of cisplatin-induced DNA crosslinks, which leads to the potentiation of cisplatin-induced cytotoxicity [12]. The use of irinotecan in gastric cancer was initially reported in Japan to have a 23% response rate, and Boku et al. [2] reported a response rate that became nearly doubled when biweekly irinotecan (70 mg/m^2) was combined with monthly cisplatin (80 mg/m^2). The toxicity of the regimen was mainly severe neutropenia, which reached up to 57% when the dose intensity of irinotecan administered was 0.81. In contrast, Ajani et al. [1] planned a weekly combination of irinotecan and cisplatin administered for 4 consecutive weeks, followed by a 2-week recovery period depending upon patients' tolerability. The incidence of grade 4 neutropenia was 15 and 66% of delayed or cancelled weekly doses occurred at the third or fourth week of each cycle [1]. The main causes of treatment delay or cancellation were diarrhea, fatigue, and neutropenia, which required high supportive care and medical costs. We concerned that a combination of cisplatin and irinotecan might induce excessive non-hematological toxicity, resulting in the deterioration of treatment compliance and quality of life. Therefore, we devised a 3-week treatment and 1-week rest schedule in order to maintain the intensity of a weekly schedule.

First, we showed an overall response rate of 25.5%. In post hoc analysis according to prior exposure to chemotherapy, the response rate was 38.3 and 20.5% among the chemotherapy-naive and chemotherapy-exposed groups, respectively. Our results showed a somewhat lower efficacy compared to previously reported phase II results, especially in chemotherapy-naive patients [1, 2, 8, 21]. Initial reports have shown a 40–50% response rate with irinotecan plus cisplatin. However, in a recently conducted larger phase II–III trial (V306) comparing irinotecan plus cisplatin versus 5-FU/folinic acid [16, 17], the response rate of an irinotecan/cisplatin combination was no more than 26% while the incidence of grade 3–4 neutropenia reached up to 56%.

Although the response rate was not so high, median survival of 44 weeks was at the highest end of survival achieved with combination chemotherapy in advanced gastric cancer. The 21-week TTP was also comparable with other reports, although not out of range. Especially of note were the results of the group who received prior chemotherapy. In this group, most patients received the first-line chemotherapy with taxanes, another choice among novel combination regimens in gastric cancer [6, 18]. Although having been exposed to an adequate dose intensity of previous taxanes (median dose intensity of taxanes, 0.91), our patients could obtain around 60% of disease control rate with 19 weeks of TTP. This suggests that our regimen could be a promising salvage treatment in palliative chemotherapy, with lack of cross-resistance to taxanes.

The main toxicity reported was neutropenia. Thirty-five percent of patients experienced grade 3–4 neutropenia. This is comparable to the study of V306, as well as other trials. Neutropenia was manageable with the

use of G-CSF. Although hematological toxicity was almost equal to that of other schedules reported, our regimen seems preferable in terms of tolerability of non-hematologic toxicity. The incidence of moderate to severe diarrhea, which had been a main obstacle in this combination, was only 4.3% in our study. Furthermore, severe fatigue was not observed in our study. Considering favorable toxicity profiles even in the second-line chemotherapy group comprising two-thirds of our patients, this combination is promising in terms of safety and tolerability.

In conclusion, fractionated irinotecan combined with cisplatin administered with 3-week-on and 1-week-off schedule produces favorable clinical benefits for patients with advanced gastric cancer. This regimen also has as feasibility as a salvage regimen, especially among patients for whom treatment with taxanes has already failed.

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