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ORIGINAL ARTICLE

Biweekly oxaliplatin, fluorouracil and leucovorin versus cisplatin, fluorouracil and leucovorin in patients with advanced gastric cancer

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Summary

Purpose: *To compare a bi-weekly infusion of leucovorin (LV) 5-fluorouracil (5-FU) for 2 days, plus oxaliplatin (LV5-FU2-oxaliplatin) and LV5-FU2-cisplatin (CDDP) regimens with respect to toxicity, objective response rates, time to progression (TTP) and overall survival (OS) in patients with advanced gastric cancer.*

Patients and methods: *Patients received LV5-FU2-oxaliplatin (oxaliplatin 85 mg/m^2, day 1; folinic acid 200 mg/m^2, days 1-2; 5-FU 400 mg/m^2, i.v. bolus, days 1-2; 5-FU 600 mg/m^2, 22-hour continuous infusion, days 1-2) or LV5-FU2-CDDP (CDDP 50 mg/m^2, day 1; plus LV5-FU2). A total of 72 patients were enrolled into this study (36 vs. 36).*

Results: *A total of 305 cycles were administered in the LV5-FU2-oxaliplatin arm (median 8) and 272 cycles in the LV5-FU2-CDDP arm (median 8). Grades 3-4 toxicity were as follows (LV5-FU2-oxaliplatin %/LV5-FU2-CDDP %; p<0.05): neutropenia 5/49, thrombocytopenia 2/6, anemia 6/16 nausea/vomiting 2/15, and mucositis 0/3. Response rate of LV5-FU2-oxaliplatin was 41% (partial response/PR 41%, stable disease/SD 31%, progressive disease/PD 28%; 95% confidence internal/95% CI 27-58) and of LV5-FU2-CDDP was 25% (PR 25%, SD 36%, PD 39%; 95% CI 14-41; p =0.013). The median TTP of the patients in the LV5-FU2-oxaliplatin arm was 8 months and 6 months for those in the LV5-FU2-CDDP arm (p=0.073). The median survival time of the patients in the LV5-FU2-oxaliplatin arm was 10 months and 7 months for those in the LV5-FU2-CDDP arm (p=0.003).*

Conclusion: *Our study showed that oxaliplatin may be substituted for cisplatin with LV5-FU2 with favorable safety and efficacy profile. The encouraging results from our study support the effectiveness of oxaliplatin-fluoropyrimidine-containing chemotherapy in gastric cancer and could provide a new core on which to add other agents in future investigations.*

Key words: advanced disease, cisplatin, gastric cancer, oxaliplatin, randomized phase II study

Introduction

The prognosis of patients with advanced gastric cancer (unresectable locoregional, relapsing and/or metastatic disease) remains poor despite of advances made over the recent decades. During the last 25 years many chemotherapeutic agents for the treatment of gastric cancer have been studied. Chemotherapy often results in symptomatic improvement with improved quality of life, but the median survival of patients with advanced disease continues to be dismal [1]. Multiple studies using a variety of chemotherapeutic agents have shown that the use of chemotherapy is clearly superior to best supportive care [2]. Nonetheless, complete responses (CRs) are rare, and PRs with single-agent chemotherapy have been limited, ranging from 0 to 30% [3]. The most widely used agent remains 5-FU with single-agent response rate ranging from 21 to 30%. The modulation of 5-FU by LV has generally enhanced antitumor efficacy (response rate 22-48%) and produced some CRs (5-9%) [4,5]. CDDP has also been associated with moderate response rate of 18 to 22% and is frequently incorporated into combination regimens. The biweekly 5-FU and LV regimen (LV5-FU2), which is

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popular in Europe [4,6], combined with low-dose CDDP was less toxic than some other 5-FU and cisplatin regimens like FUP (5-FU/cisplatin) [7], and therefore, LV5-FU2-CDDP was chosen as the reference regimen in this study.

Oxaliplatin is a third-generation cisplatin analog with a 1,2-diaminocyclohexane (DACH) carrier ligand. Its main mode of action is mediated by the formation of DACH-platinum adducts [8]. Oxaliplatin has demonstrated additive or synergistic activities with 5-FU, even in 5-FU-resistant cell lines [9]. It has also shown activity in many tumor cell lines resistant to CDDP [10]. Many studies are ongoing to test the combination of oxaliplatin and 5-FU in noncolorectal gastrointestinal tumors and other malignancies [11]. Oxaliplatin, 5-FU and LV was proved active with a 50% objective response rate in gastric cancer patients [12]. Oxaliplatin has a more favorable toxicity profile than CDDP. The dose-limiting toxicity is cumulative sensory peripheral neuropathy [11].

The aim of this study was to compare a biweekly infusion of oxaliplatin and high-dose 5-FU/LV (LV5-FU2) and LV5-FU2-CDDP regimens with respect to toxicity and objective responses in patients with advanced gastric cancer.

Patients and methods

Patients with histologically verified locally advanced and/or metastatic gastric carcinoma, without possibility for surgical resection, were eligible for the study. The diagnosis of locally advanced unresectable disease was based either on computed tomographic (CT) scan evaluation of tumor size, invasion of adjacent structures, and/or advanced locoregional node involvement, or on the findings of laparotomy. Only chemotherapy-naïve patients with measurable disease were eligible for the study. Other inclusion criteria were: ECOG performance status 0-2, age less than 72 years, normal organ functions and no contraindications for the particular drugs administration. Exclusion criteria were the following: brain metastases, concomitant second malignancy in the preceding 10 years except for basal cell skin cancer and treated *in situ* carcinoma of the cervix, uncontrolled congestive heart failure, clinically significant arrhythmia, and uncontrolled angina pectoris. Informed consent was obtained from all patients.

Patients received LV5-FU2 oxaliplatin (oxaliplatin 85 mg/m^2, day 1; folinic acid 200 mg/m^2, as 2-hour infusion, days 1-2; 5-FU 400 mg/m^2, i.v. bolus, days 1-2; 5-FU 600 mg/m^2, 22-hour continuous infusion, days 1-2; the intercycle interval was 2 weeks), or LV5-FU2-CDDP (cisplatin 50 mg/m^2, day 1; folinic acid 200 mg/m^2, as 2-hour infusion, days 1-2; 5-FU 400 mg/m^2, i.v. bolus, days 1-2; 5-FU 600 mg/m^2, 22-hour continuous infusion, days 1-2; the intercycle interval was 2 weeks). The maximum number of cycles foreseen was 12. Full doses of anticancer drugs were given if the leucocyte count was 4×10^9/L, neutrophil count 1.5×10^9/L and if the platelet count was greater than 100×10^9/L, otherwise treatment was delayed for 1 week or until complete recovery occurred. If grade 2 and 3 mucositis or diarrhea occurred, treatment was delayed for 1 week or until normalization. For grade 4 mucositis or diarrhea, patients were removed from the study. No dose reduction was allowed. The study protocol was approved by the local ethics authorities.

Prior to chemotherapy, the following examinations, related to the disease extension, were performed: clinical examination; endoscopic examination, imaging by various techniques (CT scan for abdominal, pelvic, retroperitoneal, and hepatic masses; chest X-ray and/or CT scan for lung/mediastinal lesions); serum biochemistry including liver function tests and peripheral blood count. Other examinations were performed optionally. All examinations relevant to the disease extension and size of the individual lesions were performed following every second cycle. Serum biochemistry was performed on days 1 and 15 of each cycle. Peripheral blood counts were performed on day 1 and once weekly during the intercycle interval for both arms. In cases of grade 3 or 4 hematological toxicity, peripheral blood count was performed every day until recovery from the nadir. Those patients were hospitalized. Patients with febrile neutropenia were hospitalized in bacteriological-protected unit. G-CSF was administered when needed. Each patient in this trial had passed an educational program "How to prevent yourself from infection during chemotherapy" performed by the nurses. Some of the main points of this program are: educate the patient for signs and symptoms of infection; urge the patient to maintain a safe and clean environment (avoid people who have cold or any communicable disease, do not eat raw fruits and vegetables, do not handle pet excreta, etc); emphasize the importance of meticulous personal hygiene; maintain adequate nutrition.

NCI-CTC criteria were used for toxicity grading [13]. Patients receiving 4 or more cycles were evaluable for both activity and toxicity; those receiving one cycle were evaluable for toxicity only.

Patients were evaluable for response if they had measurable lesions in two perpendicular diameters or in one dimension by ruler or calipers (e.g. metastatic pulmonary nodules surrounded by aerated lung, lymph nodes, subcutaneous masses and CT-defined liver, adrenal and lymph node metastases). CT scan was employed

for the measurement of liver metastases, abdominal masses and the primary tumor. Measurable lesions were defined as lesions of at least 2 cm in diameter. All other clinical lesions (bone metastases, ascites, malignant pleural effusion, lymphangitis or lesions of less than 2 cm in diameter) were defined as non-measurable. On the primary tumor site, patients with bidimensionally measurable disease on CT scan were required to have endoscopic evaluation with biopsy if the tumor was visible. Patients who had received radiotherapy to individual sites of disease were evaluable if they had bidimensional measurable lesions at a distance from the radiation port.

Treatment response was evaluated after every fourth cycle according to the RECIST criteria [14]. In addition, CR of the primary tumor site was defined as a normal-appearing stomach on CT scan with complete resolution of the endoscopically visible tumor and a negative biopsy of the original site of the tumor.

If CR was achieved, two additional courses were administered and the patient was then strictly monitored. Patients with PR were treated until progression, but no more than 12 courses. Patients with SD received 8 courses in total and after that they received best supportive therapy, only. In the case of PD, they received best supportive therapy. After chemotherapy completion, regular follow-up every 2 months was performed.

Independent response review was performed by members (surgeon, medical oncologist, radiologist and pathologist) of the joint interdisciplinary committee for gastrointestinal tumors of our Institute and the University Clinic for gastrointestinal diseases. The committee members were not involved in the study.

Statistical analysis

Sample size of 36 patients achieved 80% of power to detect difference of 25% in haematological toxicity between the two groups with type one error α=0.10. Descriptive statistics (mean, standard deviation, median and range) by treatment was used for continuous variables and the number and percentage for the categorical ones. Treatment differences in toxicity and response were assessed by means of chi-square/Pearson test or Fisher's exact test. TTP and OS were analyzed using the Kaplan-Meier product limit estimator. Treatment differences were investigated using the log-rank test.

Results

From August 2000 to September 2005, a total of 72 patients were enrolled. The median follow-up was 7 months (range 4-27^{+}). Thirty-six patients in the LV5-FU2-oxaliplatin arm and 36 patients in LV5-FU2-CDDP arm were analyzed for toxicity, response, TTP and OS. All of the patients had measurable disease on CT scan with or without endoscopy. The arms were well balanced in relation to age, sex distribution, previous therapy, histological grade, performance status, site of the primary tumor, site of metastases and extent of disease when treated. Patient characteristics are listed in Table 1.

Toxicity

A total of 305 cycles were administered in the LV5-FU2-oxaliplatin arm and 272 cycles in LV5-FU2-CDDP arm. The median number of the cycles administered per patient was 8 in both arms.

Myelosuppression was the most frequent side effect in LV5-FU2-CDDP arm (Table 2). In this arm, grade 3-4 neutropenia was observed in 49% of the cycles vs. 5% in LV5-FU2-oxaliplatin arm (Pearson chi-square

Table 1. Patient characteristics

Characteristic	*LV5-FU2-oxaliplatin No. of patients*	*LV5-FU2-CDDP No. of patients*
No. of patients	36	36
Median age, years (range)	57 (35-67)	55 (31-69)
Males/Females	24/12	26/10
Performance status (ECOG)		
0	3	6
1	22	20
2	11	10
Previous surgery		
Curative	22	19
Palliative	5	6
None	6	8
Sites of primary tumor		
Gastroesophageal junction	15	17
Proximal stomach	2	7
Body	11	3
Distal stomach	8	9
Histologic type		
Well differentiated	8	8
Moderately differentiated	18	20
Poorly differentiated	10	8
Site of metastases		
Liver	16	14
Abdomen/peritoneum	13	14
Lymph nodes	6	7
Lung	5	6
Bone	1	1
Local relapse	10	9
Others	1	2
Extend of disease when treated		
Locoregional advanced	2	4
Primary not resected, metastatic	4	4
Primary resected, metastatic	22	19
Locoregional recurrence	3	5
Locoregional and metastatic recurrence	7	4

Table 2. Toxicity

Parameter	LV5-FU2-oxaliplatin 305 cycles						LV5FU2-CDDP 272 cycles						Grades 3+4 p- value*
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grades 3+4 (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grades 3+4 (%)	
Hemoglobin	225	32	29	11	8	6	155	41	33	27	16	16	<0.001
Granulocytes	259	17	14	9	6	5	101	24	14	89	44	49	<0.001
Platelets	272	19	9	4	1	2	194	27	35	11	5	6	0.007
Nausea/vomiting	260	32	8	5	0	2	162	41	27	36	6	15	<0.001
Diarrhea	284	11	4	6	0	2	218	32	15	7	0	3	n.s.
Mucositis/stomatitis	287	15	3	0	0	0	221	27	15	9	0	3	0.001
Serum creatinine	289	12	4	0	0	0	225	29	18	0	0	0	n.s.
Alopecia	291	13	1	0	0	0	229	32	11	0	0	0	n.s.
Bilirubin	297	7	1	0	0	0	242	15	13	2	0	1	n.s.
Transaminases	287	11	3	4	0	2	223	34	9	6	0	2	n.s.
Alkaline phosphatase	237	49	15	4	0	1	174	72	22	4	0	1	n.s.
Heart-rhythm/function	289	14	2	0	0	0	257	12	3	0	0	0	n.s.
Neuropathy-sensory	251	29	12	13	0	4	251	8	5	8	0	3	n.s.

* Chi-square or Fisher test were used; n.s.: non significant

test; p<0.001). We recorded 19 (LV5-FU2-CDDP) and 4 (LV5-FU2-oxaliplatin arm) neutropenic febrile episodes during nadir. The difference was clinically meaningful but didn't reach statistical significance. Two of the patients with febrile neutropenia (LV5-FU2-CDDP arm) developed sepsis and died of septic shock despite antimicrobial therapy. The remaining patients recovered completely from neutropenia. Treatment-related deaths did not occur in the LV5-FU2-oxaliplatin arm.

Grade 3-4 thrombocytopenia was recorded in 6% of LV5-FU2-CDDP arm and in 2% of LV5-FU2-oxaliplatin arm cycles (Pearson chi-square test; p=0.007). No hemorrhagic manifestations were observed.

Significant differences (Pearson chi-squared test and/or Fisher exact test; p<0.01) in grade 3-4 side effects were noted for anemia (16 vs. 6%), nausea/vomiting (15 vs. 2%) and mucositis (3 vs. 0%), favoring the LV5-FU2-oxaliplatin arm. The differences in other grade 3-4 side effects were not statistically significant and were usually of short duration, reversible and easily manageable. Toxicity is listed in Table 2.

Tumor response

LV5-FU2-oxaliplatin

Confirmed objective tumor response (Table 3) was seen in 16 (41%) patients (95% CI 27-58) calculated on an intention-to-treat basis. The median duration of response was 8 months (range 4-15). Three of 16 (19%) patients with PR had secondary surgery. They achieved maximal response after 4, 4 and 6 months of treatment. Two of them had primary inoperable locally advanced gastric cancer and one of them had liver metastases with previously resected primary tumor. Successful resection in all 3 patients was performed and their TTP was 11, 14 and 7 months, respectively, while survival was 13, 18 and 12 months, respectively. Response was observed in the following disease sites: 1 of 6 (17%) primary tumors; 2 of 5 (40%) lung metastases; 6 of 16 (38%) liver metastases; 3 of 6 (50%) lymph nodes and 2 of 10 (20%) local relapses. Response was not seen in the peritoneum and in bone metastases.

Table 3. Treatment results

Response	LV 5-FU2-oxaliplatin No. of cases =36	%	LV 5-FU2-CDDP No. of cases =36	%
Complete response	0	0	0	0
Partial response	15	41	9	25
Stable disease	11	31	13	36
Progressive disease	10	28	14	39
Overall response rate	15	41	9	25
(95% confidence interval)		(27-58)		(14-41)

LV5-FU2-CDDP

Confirmed objective tumor response was seen in 9 (25%) patients (95% CI 14-41) calculated on an intention-to-treat basis. The median duration of response was 8 months (range 4-11). One of 9 patients (11%) with liver metastases and resected primary tumor, who achieved PR, had secondary surgery. He achieved maximal response after 6 months of treatment. His response duration was 11 months and survival was 15 months. Response was observed in the following disease sites: 1 of 6 (17%) lung metastases 3 of 14 (21%) liver metastases and 2 of 7 (29%) lymph nodes. Response was not seen in primary tumors, peritoneum, local relapse and bone metastases.

There was no statistical difference in response rate between the arms (Pearson chi-squared test 2.25; p=0.13).

Time to progression and survival

The median TTP of the patients in the LV5-FU2-oxaliplatin arm was 8 months and 6 months for those in the LV5-FU2-CDDP arm. Patients receiving LV5-FU2-oxaliplatin seemed to have a longer TTP, but statistical difference was not significant (log-rank; p=0.073) (Figure 1).

The median OS of the patients in the LV5-FU2-oxaliplatin arm was 10 months and 7 months for those in the LV5-FU2-CDDP arm. The difference in survival was statistically significant (log-rank; p=0.003) between the arms (Figure 2).

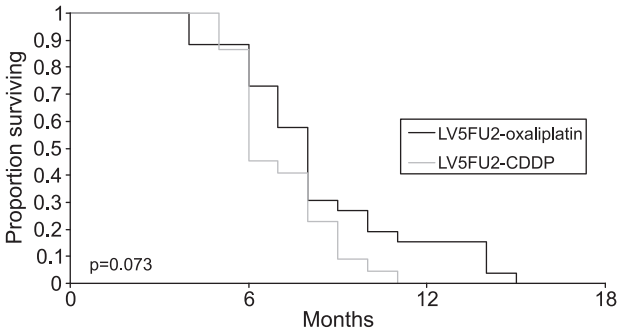

Figure 1. Time to progression.

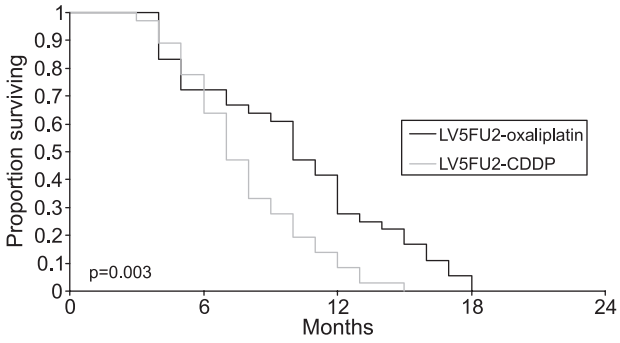

Figure 2. Overall survival.

Discussion

Although there has been a lack of consensus regarding the optimal chemotherapy for advanced gastric cancer, platinum-fluoropyrimidine doublets provide the core of many chemotherapy regimens. In the present study we compared a biweekly infusion of LV5-FU2-oxaliplatin and LV5-FU2-CDDP regimens with respect to toxicity, objective response, TTP and OS in patients with advanced gastric cancer. Our results show that LV5-FU2-oxaliplatin has had a low incidence of severe toxicity and significantly decreased the incidence of grade 3 and 4 haematological toxicity (neutropenia, thrombocytopenia, and anemia) compared to LV5-FU2-CDDP. Treatment-related deaths were not observed in the LV5-FU2-oxaliplatin arm. Of grade 3-4 non-hematological toxicity, nausea/vomiting and mucositis were frequent in the LV5-FU2-CDDP arm. The observed toxicity profile of LV5-FU2-oxaliplatin combination was very favorable in comparison with LV5-FU2-CDDP and other new generation regimens like ECF (grade 3-4 neutropenia 41.7%; grade 3-4 non-hematological toxicity 36%) [15], ECX (epirubicin/cisplatin/capecitabine; grade 3-4 neutropenia 51.1%; grade 3-4 non-hematological toxicity 33%) [15], or especially DCF (docetaxel/cisplatin/5-FU; grade 3-4 neutropenia 82%, mucositis 21%, and diarrhea 19%) where poor tolerance sometimes led to attenuation of the dosage of the original regimen [16]. LV5-FU2-oxaliplatin is also certainly easier to administer and better tolerated than DCF, which is considered to be an intensive regimen requiring growth factor support [17]. Myelosuppression, emesis and diarrhea that have been observed in patients who received ECF and DCF require inpatient administration of this regimen [15-17]. The outpatient administration of LV5-FU2-oxaliplatin is certainly advantageous in comparison to many other regimens for advanced gastric cancer.

LV5-FU2-oxaliplatin was superior to LV5-FU2-CDDP for overall response rate (41 vs. 25%) but without statistical significance, probably due to the small number of patients. We also observed advantages in TTP (median TTP 8 vs. 6 months for LV5-FU oxaliplatin and LV5-FU CDDP arms, respectively). Twenty-eight percent vs. 39% of the patients on LV5-FU2-oxaliplatin and LV5-FU2-CDDP arms, respectively, had

early disease progression and those results influenced survival. Three months difference in survival favoring the LV5-FU2-oxaliplatin arm could explain the observed differences on TTP and early progressions. The activity of oxaliplatin-based chemotherapy in gastric cancer is further supported by the results of several phase II studies. When administered as first-line chemotherapy for advanced or metastatic gastric cancer, regimens which consist of oxaliplatin/5-FU/LV applied in different schedules and doses have demonstrated response rates of 38 to 55%, median TTP of 4.9 to 7.7 months and median overall survival of 8 months to 11.4 months [3,4,18,19]. However, we can not predict which oxaliplatin-based regimen will be superior without results of randomized studies comparing different oxaliplatin-based protocols.

In order to improve the efficacy of chemotherapy in advanced gastric cancer, 3 drug regimens were tested in randomized studies. ECF is widely used in the UK for the treatment of advanced gastric cancer, having demonstrated superiority to both FAMTX (5-FU/doxorubicin/methotrexate) and MCF (mitomycin/CDDP/5-FU) [20] in patients with previously untreated advanced disease. In two randomized phase III studies [1,20], ECF demonstrated overall response rate of 46 and 42%, and median overall survival of 8.7 and 9.4 months. Using ECF as a reference regimen the phase III REAL-2 study was conducted to compare oxaliplatin with CDDP, and also 5-FU with capecitabine in patients with advanced disease. Analysis of data for each of the 4 treatment regimens showed median overall survival of 9.9 months for ECF, 9.3 months for EOF (epirubicin/oxaliplatin/5-FU), 9.9 months for epirubicin/cisplatin/capecitabine (ECX), and 11.2 months for EOX (epirubicin/oxaliplatin/capecitabine) [15]. The survival benefit for EOX compared to ECF was statistically significant. Response rates were consistently high at 40.7, 46.4, 42.4 and 47.9% for ECF, ECX, EOF and EOX, respectively, with no significant difference between the groups. The authors concluded that oxaliplatin may be substituted for CDDP in ECF and that EOX seems to be associated with significantly improved efficacy compared to ECF. Based on the results of the previously mentioned studies, as well as on our results, it looks like oxaliplatin could be established as the optimal platinum agent in gastric cancer.

The results of the TAX 325 study have brought out the role of docetaxel in advanced gastric cancer [16]. In this large phase III study, docetaxel/cisplatin/5-FU (DCF) achieved a median TTP of 5.6 months, a median overall survival of 9.2 months and a response rate of 37%. All of these parameters were significantly improved compared with the reference regimen CDDP/5-FU. As mentioned previously in the discussion, DCF efficacy in TAX 325 study was accompanied with significant toxicity. Novel cytotoxic combinations of docetaxel plus oxaliplatin will be of interest. Taking a deeper view to TAX 325 study and our study, the docetaxel-LV5-FU2-oxaliplatin should be investigated in patients with advanced gastric cancer.

Conclusion

A number of active agents are now available for the treatment of advanced gastric cancer. The newer agents, such as oxaliplatin, capecitabine, and docetaxel, offer the potential to build on established strategies, in particular platinum-fluoropyrimidine combinations, and to improve both efficacy and tolerability of chemotherapy. Our study showed that oxaliplatin may be substituted for CDDP (LV5-FU2-oxaliplatin) with favorable safety and efficacy. The encouraging results from our study support the potential of oxaliplatin-fluoropyrimidine-containing chemotherapy in gastric cancer and could provide a new core on which to add other agents, such as docetaxel and biological agents, in future investigations.

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