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ORIGINAL ARTICLE

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Phase I combination trial of gemcitabine, paclitaxel, and carboplatin in patients with advanced malignancy

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Abstract *Purpose*: We performed a phase I trial of carboplatin and paclitaxel in combination with gemcitabine in order to determine the tolerability of this triplet. *Methods*: Enrolled in the study were 26 patients with advanced cancer, most with non-small cell lung cancer. The patients received escalating doses of carboplatin and paclitaxel on day 1 and gemcitabine (30-min infusion) on days 1, 8, and 15 of a 28-day treatment cycle. The doses of each drug ranged from an area under the concentration-time curve (AUC) of 5 to 6 for carboplatin, 135 to 175 mg/m^2 for paclitaxel, and 300 to 1000 mg/m^2 for gemcitabine. *Results*: Hematologic toxicity was the most commonly observed toxicity and was dose-limiting. During the first cycle at the recommended phase II dose, there were two instances of grade 4 neutropenia and one instance of grade 4 thrombocytopenia among six patients, none of which was dose-limiting. Cumulative hematologic toxicity emerged in subsequent cycles. Non-hematologic toxicities were mild. Five patients, all with previously untreated non-small-cell lung cancer (NSCLC), had a partial response. Nine patients with NSCLC or upper gastrointestinal malignancies experienced stable disease. *Conclusions*: Based on significant neutropenia and thrombocytopenia, the regimen recommended for further study consists of carboplatin AUC 5, paclitaxel 175 mg/m^2, and gemcitabine 1000 mg/m^2 on a 28-day cycle. The antitumor activity noted suggests that further investigation of this well-tolerated combination in specific tumor types, especially NSCLC, is warranted.

Keywords Chemotherapy · Clinical trial · Phase I · Lung cancer

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Introduction

For patients with advanced ovarian, small and non-small-cell lung (NSCLC), head and neck, and urothelial cancers, platinum-based chemotherapy is the current standard [1, 2, 3, 4]. However, response rates and prolongation of survival with chemotherapy are modest. In two recent large randomized trials, four doublet regimens used in the treatment of NSCLC were compared, and carboplatin and paclitaxel was found to be the best tolerated [5, 6], allowing for the combination with other novel agents. Three-drug chemotherapy combinations have shown higher response rates for certain solid tumors, raising the possibility of improved survival compared to conventional doublets. The combination of 5-fluorouracil, irinotecan, and oxaliplatin in colorectal cancer is a recent example [7].

Gemcitabine is a deoxycytidine analog with single-agent activity against (NSCLC) [8, 9, 10], as well as breast, small-cell lung, prostate and pancreatic carcinomas [11]. In vitro synergy between gemcitabine- and platinum-containing chemotherapy has been shown [12, 13, 14]. The combination of gemcitabine and carboplatin has also demonstrated synergism in vitro, with no dependence on the sequence of administration [15]. The addition of paclitaxel to gemcitabine and carboplatin further augments the antiproliferative effect. In a four-arm NSCLC trial, treatment with gemcitabine and cisplatin was well tolerated and associated with a statistically significant prolongation in median time to progression compared to the other three regimens [4].

Other than myelosuppression, there are no overlapping toxicities that would preclude the combination of

these drugs in vivo. Several recent studies of triplet combinations have shown higher response rates than those seen with standard doublet regimens in previously treated breast and NSCLC [16, 17, 18]. We performed a phase I trial of gemcitabine, carboplatin and paclitaxel in patients with advanced malignancies in order to evaluate the tolerability of this regimen.

Materials and methods

Eligible patients for this trial had histologically confirmed advanced solid tumors, with either measurable or evaluable disease. Adequate baseline bone marrow and organ function were defined as follows: absolute neutrophil count (ANC) $\geq 1500/mm^3$, platelet count $\geq 100{,}000/mm^3$, white blood count $\geq 3000/mm^3$, serum creatinine ≤ 1.5 mg/dl, serum bilirubin ≤ 1.5 mg/dl, SGOT/SGPT not more than five times the upper limit of normal, and electrolytes within 10% of the upper and lower limit of normal. Patients were at least 18 years of age with an ECOG performance status of 0 or 1. Fertile participants were required to use adequate contraception. All patients were given information on the purpose and conduct of this study, and signed written informed consent in accordance with federal, state, and institutional guidelines.

Treatment with either chemotherapy or radiotherapy within 3 weeks of enrollment was not allowed. In the case of nitrosoureas or mitomycin C, 6 weeks must have elapsed since the most recent treatment. Patients had to have recovered from the acute effects of any prior therapy. Active infection or significant medical problem that might limit the individual's ability to receive treatment were not permitted.

Patients were treated according to the following schedule: sequential paclitaxel, carboplatin, and gemcitabine were administered intravenously on day 1 of a 28-day cycle, followed by gemcitabine alone on days 8 and 15. Patients were instructed to take 12 mg of oral dexamethasone 12 and 6 h prior to their scheduled infusions on day 1 of each cycle to prevent hypersensitivity reactions to paclitaxel. Patients were given another 12 mg oral dexamethasone 30 min prior to the infusion of paclitaxel, in addition to 25 mg diphenhydramine and 400 mg cimetidine, 150 mg ranitidine, or 150 mg nizatidine orally. Paclitaxel was administered first as an infusion in 250 ml normal saline over 3 h. Carboplatin was administered second as a 30-min infusion in 100 ml normal saline. Each patient's glomerular filtration rate was estimated using the Cockcroft-Gault method [19]. The dose of carboplatin was calculated with the formula of Calvert et al. [20] and is expressed in terms of the area under the concentration-time curve (AUC). Gemcitabine was administered third as a 30-min infusion in 100 ml normal saline. For dose level 1, the doses of each drug in the combination were reduced out of concern for the possibility of additive hematologic toxicity if full doses of each drug were given. The dose of gemcitabine was reduced by a greater percentage than those of the other drugs, because carboplatin and paclitaxel were felt to be the principal components of the regimen.

Dose-limiting toxicity (DLT) was defined as any one of the following during the first cycle: (1) an ANC less than $500/mm^3$ or platelet count less than $50{,}000/mm^3$ for more than 5 days; (2) ANC less than $500/mm^3$ with fever requiring antibiotics; or (3) non-hematologic toxicity of at least grade 3 using the Common Toxicity Criteria. The maximum tolerated dose (MTD) was defined as one dose level below the level that induced DLT in more than one-third of patients. This MTD definition allowed a 33% severe toxicity rate which is typically seen with the combination of carboplatin and paclitaxel [6]. The last patient enrolled to a given dose level was observed for at least 2 weeks, the time when blood counts show a nadir with carboplatin and paclitaxel, prior to enrolling patients to a higher dose level. A 25% dose reduction of all three drugs was made if the ANC was less than $500/mm^3$ for more than 5 days, was ever less than $100/mm^3$, or if the platelet count was ever less than $25{,}000/mm^3$. On days 8 and 15 of each cycle, gemcitabine was not administered if the ANC was $1500/mm^3$ or less or the platelet count was $100{,}000/mm^3$ or less.

Each dose level was intended to accrue three patients. In the event of DLT in one or two of the three patients, provision was made to accrue an additional three patients to that dose level. If three or more patients experienced a DLT, then the previous dose level was determined to be the MTD. An additional patient was added to dose level 3, as this patient required prompt treatment and the next dose level had not yet opened for accrual.

Prior to initiation of therapy, each patient was evaluated with a history, physical examination, tumor measurement using an appropriate radiographic technique, assessment of ECOG performance status, complete blood count with differential and serum chemistries. Complete blood counts were performed twice weekly and serum chemistries weekly during the first cycle, with more frequent monitoring in the event of myelosuppression. Each of these, with the exception of tumor measurement was performed prior to the administration of each subsequent cycle. Pharmacokinetic analysis of carboplatin in whole plasma was planned, but was not pursued by the sponsor.

Patients were evaluated for response after every other treatment cycle using WHO criteria [21]. A complete response was defined as complete disappearance of all measurable and evaluable disease for at least 4 weeks without the appearance of new lesions. A partial response was defined as a decrease of 50% or more in the sum of the products of the perpendicular diameters of all measurable lesions without the appearance of new lesions. Stable disease was defined as no change or less than 25% increase or decrease in the size of indicator lesions. Progressive disease was defined as an increase of 25% or more in the ratio of the sum of the products of the perpendicular diameters of all measurable lesions to the smallest sum observed. Clear worsening of evaluable disease or the appearance of any new lesions was also considered progressive disease.

Results

Patient demographics

A total of 26 patients were enrolled in the study at the Thomas Jefferson University Kimmel Cancer Center and the University of Pennsylvania Cancer Center (Table 1). The baseline characteristics of these patients are presented in Table 1. The majority of the patients had NSCLC and had received no prior therapy. ECOG performance status was nearly equally divided between 0 and 1. The majority of participants had received no prior chemotherapy; therefore, this was a good-risk population of patients.

Toxicity

As a result of one hematologic and one non-hematologic DLT during the first cycle in the first and second of three patients enrolled at dose level 1, a new dose level (−1) was designated with a 25% reduced dose of gemcitabine (Table 2). Seven patients were accrued to this dose level after the first patient experienced dose-limiting neutropenia and one patient did not complete the first cycle. Based on data emerging from a concurrent phase I trial of this combination, the safety of dose level 1 was felt to be well-established. Subsequently, dose escalation

Table 1 Baseline characteristics

Total patients enrolled	26
Male	15
Female	11
Age (years)	
Median	52
Range	33–70
ECOG performance status	
0	14
1	12
Primary disease site	
Lung	16
Gastric	3
Esophageal	2
Gastro-esophageal junction	1
Bile duct	1
Gallbladder	1
Mesothelioma	1
Bladder	1
Prior treatments	
None	16
Chemotherapy	16
Radiation therapy	1
Chemotherapy and radiation	3

resumed at dose level 2. Three, four, and three patients were accrued to dose levels 2, 3, and 4, respectively, without observing DLT.

At dose level 5, the first patient experienced dose-limiting febrile neutropenia and grade 4 thrombocytopenia requiring hospitalization. The second and third patients developed grade 3 thrombocytopenia, lasting fewer than 5 days, in the first cycle. Cumulative hematologic toxicity also became evident. Whereas grade 3 or 4 neutropenia developed in two of six patients in the first cycle at dose level 4, five of six patients developed that degree of toxicity over subsequent cycles. Data emerging from two other phase I trials with this combination also confirmed that dose level 5 was associated with unacceptable hematologic toxicity [22, 23]. Three additional patients were accrued to dose level 4 without DLTs in the first cycle. This dose level was deemed suitable for phase II study based on the absence of early DLT in any of the six patients treated at this level. In the cohort treated by Kelly et al., 21 patients were treated at this level, which established with reasonable confidence that the fourth dose level was an appropriate starting dose with this regimen [23].

The most frequent toxicity was hematologic (Tables 3 and 4). In the first cycle, there were eight instances of grade 4 neutropenia (31% of all first cycles), two of which were dose-limiting based on a duration of greater than 5 days. At the top two dose levels, 33% of first cycles were complicated by grade 4 neutropenia, of which one instance was dose-limiting. There were two occurrences (8%) of grade 4 thrombocytopenia in the first cycle, one of which was dose-limiting. Both occurred at the top two dose levels. Grade 2 or 3 anemia was observed in 19% of patients during the first cycle. At the recommended phase II dose, the dose of gemcitabine was reduced by 20% at the beginning of the second cycle for two patients. There were no delays in the administration of the second cycle. Across all dose levels, the neutrophil and platelet nadir occurred between day 15 and day 22.

After repeated treatment, the rate of severe myelosuppression increased, particularly at the top two dose levels where 1000 mg/m^2 of gemcitabine was adminis-

Table 2 Dose-escalation scheme

Dose level	No. of patients	Carboplatin (AUC)	Paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
−1	7	5	135	300
1	3	5	135	400
2	3	5	135	800
3	4	5	135	1000
4	6	5	175	1000
5	3	6	175	1000

Table 3 Hematologic toxicity—first cycle. Values in parentheses are the number of dose-limiting toxicities (*G* gemcitabine, mg/m^2; *P* paclitaxel, mg/m^2; *C* carboplatin, AUC)

Dose level		Patients per dose level	Number of events								
			Neutropenia			Anemia			Thrombocytopenia		
			Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
(−1)	G 300, P 135, C 5	7	0	1	3 (1)	0	0	0	3	0	0
1	G 400, P 135, C 5	3	1	0	1	0	1	0	0	1	0
2	G 800, P 135, C 5	3	0	1	0	0	1	0	0	1	0
3	G 1000, P 135, C 5	4	1	2	1	1	0	0	1	3	0
4	G 1000, P 175, C 5	6	2	0	2	0	0	0	0	1	1
5	G 1000, P 175, C 6	3	0	1	1 (1)	2	0	0	0	2	1 (1)
Totals		26	4	5	8	3	2	0	4	7	2

Table 4 Hematologic toxicity—all cycles (*G* gemcitabine, mg/m^2; *P* paclitaxel, mg/m^2; *C* carboplatin, AUC)

Dose level		Number of cycles	Percentage of events								
			Neutropenia			Anemia			Thrombocytopenia		
			Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
(−1)	G 300, P 135, C 5	14	7	14	14	0	0	0	14	14	0
1	G 400, P 135, C 5	8	13	0	13	0	13	0	0	13	0
2	G 800, P 135, C 5	10	10	20	10	10	10	0	10	20	0
3	G 1000, P 135, C 5	21	14	29	19	29	0	0	38	19	5
4	G 1000, P 175, C 5	31	23	23	26	52	10	0	13	10	13
5	G 1000, P 175, C 6	11	18	36	36	82	0	0	9	45	27
Totals		95	16	22	21	34	5	0	17	18	8

tered. At the top two dose levels, 44% of first cycles were complicated by grade 3/4 neutropenia. Even after dose reductions, 58% of subsequent cycles were associated with grade 3/4 neutropenia. Grade 4 thrombocytopenia occurred in 15% of first cycles and 15% of subsequent cycles. The rate of grade 2/3 anemia was 22% in the first cycle and 79% in subsequent cycles. There was one case of febrile neutropenia at dose level 5.

At the recommended phase II dose, there was no dose-limiting hematologic toxicity in the first cycle. As noted above, there was evidence of cumulative neutropenia (Tables 3 and 4). Non-dose-limiting grade 4 neutropenia was seen in 26% of cycles, a degree that is consistent with the usual treatment of NSCLC and ovarian cancer with carboplatin and paclitaxel [4].

There were no grade 3 or 4 symptomatic non-hematologic toxicities related to treatment. Alopecia, fatigue (seven instances of grade 2), and nausea (five instances of grade 2) were most common. Five patients developed grade 1 neuropathy. Asymptomatic and transient hyperglycemia and elevated liver transaminases were the most commonly observed laboratory abnormalities, with five instances of grade 3 toxicity. One patient with a history of congestive heart failure experienced grade 3 congestive heart failure that responded to diuresis and was likely related to fluid overload from intravenous hydration received during therapy.

Clinical response

Of the 26 patients, 23 were evaluable for response. At dose levels 3 and 4, seven of ten patients had previously untreated NSCLC. Five of these patients had a partial response, two at dose level 3 and three at dose level 4. One other patient had stable disease for ten cycles. Of the five responders, two continued receiving treatment for eight cycles, two for four, and one for three. One of the patients who had a partial response after four cycles was removed from the study in order to receive consolidation therapy with radiation and additional cycles of carboplatin and paclitaxel. Disease stability lasting for more than two cycles was observed in an additional eight patients, four with NSCLC and the others with mesothelioma, cholangiocarcinoma, gastric cancer, and adenocarcinoma of the gastro-esophageal junction. Three of these patients continued to receive treatment for six, eight and ten cycles.

Discussion

We performed a dose-escalation study of carboplatin, paclitaxel and gemcitabine in order to determine the MTD of the combination. Using a 28-day treatment cycle, all three drugs were administered on day 1 and gemcitabine was given again on days 8 and 15. Based on hematologic DLT at dose level 5, we identified carboplatin at an AUC of 5, paclitaxel at 175 mg/m^2, and gemcitabine at 1000 mg/m^2 as the MTD. At those doses, there was a 26% incidence of grade 4 neutropenia.

The combination of carboplatin, paclitaxel and gemcitabine given as a 21-day cycle has been evaluated in two previously reported dose-escalation studies. Hainsworth et al. performed a dose-escalation and efficacy trial in patients with NSCLC at the Sarah Cannon-Minnie Pearl Cancer Center [22]. All three drugs were administered on day 1 and gemcitabine was given again on day 8. In the phase I portion of the trial the dose of paclitaxel was fixed at 200 mg/m^2. The first dose level consisted of carboplatin at an AUC of 6 and gemcitabine at 800 mg/m^2, in addition to paclitaxel. Thrombocytopenia precluded administration of the day-8 dose of gemcitabine in several of the seven patients at the first dose level. Therefore, a second dose level was created with a lower dose of carboplatin (AUC 5), and a higher dose of gemcitabine (1000 mg/m^2). Eight patients were treated at this level. The percentage of the planned dose of gemcitabine given increased in the second dose level compared to the first. In the phase II portion of the study, using the second dose level, 69 additional chemotherapy-naive patients with stage IIIB or IV NSCLC were treated. Of these patients, 48% experienced grade 3 or 4 leukopenia and 45% developed grade 3 or 4 thrombocytopenia. Of 77 evaluable patients, 2 had a complete response (2.6%) and 32 had a partial response (41.6%).

Kelly et al. evaluated the combination of carboplatin, paclitaxel and gemcitabine in a phase I/II trial at

the University of Colorado [23], in which 51 patients who had not received prior chemotherapy for stage IIIB or IV NSCLC were enrolled. The first three dose levels called for carboplatin at an AUC of 6. Five patients were to be enrolled at each dose level. Grade 3 or 4 thrombocytopenia occurred during the fourth, fifth, and sixth cycles in 4 of the 14 patients accrued to those levels, prompting a reduction in the dose of carboplatin (AUC 5) for subsequent dose levels. The doses of paclitaxel and gemcitabine were escalated from 175 to 200 mg/m^2 and 600 to 1000 mg/m^2, respectively. Dose-limiting thrombocytopenia occurred with carboplatin at AUC 5, paclitaxel at 200 mg/m^2, and gemcitabine at 1000 mg/m^2. A total of 21 patients were treated at the recommended phase II doses of carboplatin (AUC 5), paclitaxel (175 mg/m^2), and gemcitabine (1000 mg/m^2). Grade 3 or 4 neutropenia complicated 34% of cycles. Grade 3 or 4 thrombocytopenia occurred in 15% of all cycles. Of 47 evaluable patients, 10 (21%) had a partial response.

Phase II trials with carboplatin, paclitaxel and gemcitabine have been performed in carcinoma of unknown primary, bladder cancer, and NSCLC [24, 25, 26]. These studies confirmed the safety of the recommended doses in our study. Furthermore, response rates exceeded those seen with conventional two-drug combinations. A phase III clinical trial was performed comparing carboplatin and paclitaxel to carboplatin, paclitaxel, and gemcitabine in NSCLC [27]. The first phase of the study found a superior response rate with the three-drug combination with acceptable toxicity; overall survival was the primary endpoint of this trial.

There are no previous reports of this drug combination administered over a 28-day treatment cycle. Gemcitabine was administered 3 out of 4 weeks in this schedule as opposed to 2 out of 3 weeks in the previously described combinations [22, 23]. Despite this difference in schedule, the recommended phase II doses of each drug are the same as those recommended by Kelly et al. [23]. The dose of paclitaxel was 14% higher in the recommended phase II regimen reported by Hainsworth et al. [22]. The hematologic and non-hematologic toxicities of the 28-day and 21-day cycles appear similar. Experience with gemcitabine in combination with other agents suggests that a 21-day cycle may be associated with less myelosuppression, particularly thrombocytopenia [28, 29]. However, the 21-day and 28-day schedules have not been compared head-to-head. Multiple phase I studies are important in the development of combination chemotherapy regimens. The MTD can be heavily influenced by patient heterogeneity and small sample size. This can result in significantly different outcomes between similarly designed trials, as was the case with phase I trials of 5-fluorouracil and gemcitabine [30, 31].

Neutropenia and thrombocytopenia were the predominant severe toxicities associated with this regimen. Anemia became more severe after repeated cycles. Our data are most similar to those of Kelly et al., in that severe neutropenia was nearly twice as common as severe thrombocytopenia. Hainsworth et al. reported a nearly equal incidence of neutropenia and thrombocytopenia. In part, this can be explained by the fact that Hainsworth et al. evaluated two dose levels versus six levels in both our study and that of Kelly et al. [23]. Therefore, more patients were treated at or near the recommended phase II dose by Hainsworth et al. [22]. Both of the previous studies were limited to patients with NSCLC who had not received prior chemotherapy. Of 16 patients with NSCLC in our study, 5 (31%) had partial responses. Stable disease was observed in several other tumor types.

We conclude that the triplet of carboplatin, paclitaxel and gemcitabine is well tolerated at the recommended doses and is associated with significant activity in NSCLC. Hematologic toxicity is dose-limiting, but other side effects were not severe. Phase II evaluation of this regimen is warranted in several tumor types.

References

1. Vermorken JB (2001) The integration of paclitaxel and new platinum compounds in the treatment of advanced ovarian cancer. Int J Gynecol Cancer 11 [Suppl 1]:21–30
2. Sandler A (2000) Chemotherapy in metastatic non-small-cell lung cancer. Oncology (Huntingt) 14 [7 Suppl 5]:15–27
3. Waxman J, Wasan H (1994) Platinum-based chemotherapy for bladder cancer. Semin Oncol 21 [5 Suppl 12]:54–60
4. Forastiere AA (1994) Overview of platinum chemotherapy in head and neck cancer. Semin Oncol 21 [5 Suppl 12]:20–27
5. Kelly K, Crowley J, Bunn PA Jr, Presant CA, Grevstad PK, Moinpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK, Livingston RB, Gandara DR (2001) Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 19:3210–3218
6. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH; The Eastern Cooperative Oncology Group (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–98
7. Souglakos J, Mavroudis D, Kakolyris S, Kourousis Ch, Vardakis N, Androulakis N, Agelaki S, Kalbakis K, Tsetis D, Athanasiadis N, Samonis G, Georgoulias V (2002) Triplet combination with irinotecan plus oxaliplatin plus continuous-infusion fluorouracil and leucovorin as first-line treatment in metastatic colorectal cancer: a multicenter phase II trial. J Clin Oncol 20:2651–2657
8. Cormier Y, Eisenhauer E, Muldal A, Gregg R, Ayoub J, Goss G, Stewart D, Tarasoff P, Wong D (1994) Gemcitabine is an active new agent in previously untreated extensive small cell lung cancer (SCLC). A study of the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol 5:283–285
9. Abratt RP, Bezwoda WR, Falkson G, Goedhals L, Hacking D, Rugg TA (1994) Efficacy and safety profile of gemcitabine in non-small-cell lung cancer: a phase II study. J Clin Oncol 12:1535–1540
10. Anderson H, Lund B, Bach F, Thatcher N, Walling J, Hansen HH (1994) Single-agent activity of weekly gemcitabine in advanced non-small-cell lung cancer: a phase II study. J Clin Oncol 12:1821–1826
11. Guchelaar HJ, Richel DJ, van Knapen A (1996) Clinical, toxicological and pharmacological aspects of gemcitabine. Cancer Treat Rev 22:15–31

12. Peters GJ, Bergman AM, Ruiz van Haperen VW, Veerman G, Kuiper CM, Braakhuis BJ (1995) Interaction between cisplatin and gemcitabine in vitro and in vivo. Semin Oncol 22 [4 Suppl 11]:72–79
13. Kanzawa F, Saijo N (1997) In vitro interaction between gemcitabine and other anticancer drugs using a novel three-dimensional model. Semin Oncol 24 [2 Suppl 7]:S8–S16
14. Bergman AM, Ruiz van Haperen VW, Veerman G, Kuiper CM, Peters GJ (1996) Synergistic interaction between cisplatin and gemcitabine in vitro. Clin Cancer Res 2:521–530
15. Edelman MJ, Quam H, Mullins B (2001) Interactions of gemcitabine, carboplatin and paclitaxel in molecularly defined non-small-cell lung cancer cell lines. Cancer Chemother Pharmacol 48:141–144
16. Baldini E, Ardizzoni A, Prochilo T, Cafferata MA, Boni L, Tibaldi C, Neumaier C, Conte PF, Rosso R; Italian Lung Cancer Task Force (2001) Gemcitabine, Ifosfamide and Navelbine (GIN): activity and safety of a non-platinum-based triplet in advanced non-small-cell lung cancer (NSCLC). Br J Cancer 85:1452–1455
17. Frasci G, D'Aiuto G, Comella P, Thomas R, Capasso I, Botti G, Cortino GR, Di Bonito M, Rubulotta R, Vallone P, Comella G (2002) A phase I-II study on a gemcitabine-cyclophosphamide-fluorouracil/folinic acid triplet combination in anthracycline- and taxane-refractory breast cancer patients. Oncology 62:25–32
18. Comella P, Frasci G, Panza N, Manzione L, De Cataldis G, Cioffi R, Maiorino L, Micillo E, Lorusso V, Di Rienzo G, Filippelli G, Lamberti A, Natale M, Bilancia D, Nicolella G, Di Nota A, Comella G (2000) Randomized trial comparing cisplatin, gemcitabine, and vinorelbine with either cisplatin and gemcitabine or cisplatin and vinorelbine in advanced non-small-cell lung cancer: interim analysis of a phase III trial of the Southern Italy Cooperative Oncology Group. J Clin Oncol 18:1451–1457
19. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
20. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748–1756
21. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214
22. Hainsworth JD, Burris HA 3rd, Erland JB, Morrissey LH, Meluch AA, Kalman LA, Hon JK, Scullin DC Jr, Smith SW, Greco FA (1999) Phase I/II trial of paclitaxel by 1-hour infusion, carboplatin, and gemcitabine in the treatment of patients with advanced nonsmall cell lung carcinoma. Cancer 85:1269–1276
23. Kelly K, Mikhaeel-Kamel N, Pan Z, Murphy J, Prindiville S, Bunn PA Jr (2000) A phase I/II trial of paclitaxel, carboplatin, and gemcitabine in untreated patients with advanced non-small cell lung cancer. Clin Cancer Res 6:3474–3479
24. Greco FA, Hainsworth JD, Yardley DA, Burris HA III, Erland JB, Rodriguez GI, Shaffer DW (2002) Sequential paclitaxel/carboplatin/etoposide (PCE) followed by irinotecan/gemcitabine for patients (pts) with carcinoma of unknown primary site (CUP): a Minnie Pearl Cancer Research Network phase II trial (abstract 642). Proceedings of the Annual Meeting of the American Society of Clinical Oncology
25. Vaishampayan U, Smith D, Redman B, Kucuk O, Ensley J, Hussain M (1999) Phase II evaluation of carboplatin, paclitaxel and gemcitabine in advanced urothelial carcinoma (abstract). Proceedings of the Annual Meeting of the American Society of Clinical Oncology
26. Favaretto A, Paccagnella A, Oniga F, Tumolo S, Barbieri F, Ceresoli G, Gulisano M, Schiavon S (2000) Paclitaxel and carboplatin in combination with gemcitabine (PCG): a phase I-II trial in non-small cell lung cancer (NSCLC) (abstract 2003). Proceedings of the Annual Meeting of the American Society of Clinical Oncology
27. Paccagnella A, Favaretto A, Bearz A Frustaci S, Barbieri F, Oniga F, Ghi MG, Biason R, Clerici MP, Ceresoli G, Chella A, Riccardi A (2002) Carboplatin/paclitaxel (CP) vs carboplatin/paclitaxel/gemcitabine (CPG) in advanced NSCLC: a phase II-III multicentric study (abstract 1349). Proceedings of the Annual Meeting of the American Society of Clinical Oncology
28. Rosell R, Tonato M, Sandler A (1998) The activity of gemcitabine plus cisplatin in randomized trials in untreated patients with advanced non-small cell lung cancer. Semin Oncol 25 [4 Suppl 9]:27–34
29. Langer CJ, Gandara DR, Calvert P, Edelman MJ, Ozols RF (1999) Gemcitabine and carboplatin in combination: an update of phase I and phase II studies in non-small cell lung cancer. Semin Oncol 26 [1 Suppl 4]:12–18
30. Berlin JD, Alberti DB, Arzoomanian RZ, Feierabend CA, Simon KJ, Binger KA, Marnocha RM, Wilding G (1998–99) A phase I study of gemcitabine, 5-fluorouracil and leucovorin in patients with advanced, recurrent, and/or metastatic solid tumors. Invest New Drugs 16:325–330
31. Poplin E, Roberts J, Tombs M, Grant S, Rubin E (1999) Leucovorin, 5-fluorouracil, and gemcitabine: a phase I study. Invest New Drugs 17:57–62