Cancer Chemother Pharmacol (2004) 53: 404–408
DOI 10.1007/s00280-003-0754-1

ORIGINAL ARTICLE

Keith T. Flaherty · James P. Stevenson
Maryann Redlinger · Kenneth M. Algazy
Bruce Giantonio · Peter J. O'Dwyer

A phase I, dose escalation trial of ZD0473, a novel platinum analogue, in combination with gemcitabine

Received: 8 September 2003 / Accepted: 19 November 2003 / Published online: 29 January 2004

Abstract *Purpose*: To develop a combination regimen for clinical testing, we performed a dose escalation study of ZD0473 in combination with gemcitabine. ZD0473 is a novel platinum analogue with an aliphatic cyclic carrier ligand. In vitro and in vivo studies suggest that it possesses a different spectrum of antitumor activity from cisplatin and carboplatin. In single-agent studies of ZD0473, myelosuppression was the predominant toxicity and responses were observed. *Methods*: In this combination phase I trial, 36 patients with advanced cancer were accrued to four dose levels, with doses of ZD0473 and gemcitabine ranging from 60 to 120 mg/m^2 and 600 to 750 mg/m^2, respectively. ZD0473 was administered on day 1 and gemcitabine was given on days 1 and 8 of a 21-day cycle. *Results*: Hematologic toxicity was dose-limiting. Grade 3 and 4 thrombocytopenia and neutropenia occurred during 60% and 41% of all cycles. Nonhematologic toxicities were mild and reversible. Two partial responses and 19 patients with stable disease were observed. *Conclusions*: The recommended phase II doses are 90 mg/m^2 of ZD0473 and 750 mg/m^2 of gemcitabine for lightly pretreated patients and 600 mg/m^2 for heavily pretreated patients. The combination of ZD0473 and gemcitabine is associated with dose-dependent thrombocytopenia and neutropenia as well as having promising clinical activity.

Keywords ZD0473 · Platinum analogue · Gemcitabine · Phase I trial

K. T. Flaherty (✉) · J. P. Stevenson · M. Redlinger
K. M. Algazy · B. Giantonio · P. J. O'Dwyer
Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA
E-mail: ktflaherty@aol.com
Tel.: +1-215-6628624
Fax: +1-215-2433269

K. T. Flaherty
Abramson Cancer Center of the University of Pennsylvania, Medical Arts Building, Suite 103, 39th & Market Streets, Philadelphia, PA 19104, USA

Introduction

In the effort to broaden the spectrum of malignancies susceptible to platinum-based chemotherapy and to prolong the duration of responses, the circumvention of platinum resistance continues to be of considerable interest. Several mechanisms account for primary or acquired resistance to platinum analogues [1]. The upregulation of glutathione is one means by which cells can reduce DNA-targeted electrophiles such as cisplatin [2]. Previous work with inhibitors of glutathione synthesis have sought to modify this mechanism [3].

ZD0473 [*cis*-amminedichloro(2-methylpyridine)platinum(II)] is a novel platinum complex that is sterically hindered from reacting with thiol-containing species. In vitro data demonstrate a significantly lower IC_{50} and greater intracellular drug accumulation than cisplatin or carboplatin in resistant ovarian cancer cell lines [4]. This distinction persists in a cell line with fivefold increased intracellular glutathione concentrations. ZD0473 has shown activity against human leukemia and ovarian carcinoma xenografts in mice [5]. Two phase I clinical trials have shown ZD0473 to have good tolerability in humans associated with dose-dependent hematologic toxicity [6, 7]. Responses in various solid tumors have been described in the phase I studies.

Gemcitabine is a deoxycytidine analogue with single-agent activity against non-small-cell lung cancer (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], and such combinations represent standard therapy in several solid malignancies [15, 16].

We performed a phase I clinical trial to evaluate the safety of the combination of ZD0473 and gemcitabine. ZD0473 was given on day 1 and gemcitabine was administered on days 1 and 8 of a 21-day cycle.

Patients and methods

Eligible patients had histologically confirmed, advanced solid tumors. They could have either measurable or evaluable disease. Adequate baseline bone marrow and organ function were defined as follows: absolute neutrophil count (ANC) $\geq 1500/mm^3$, hemoglobin ≥ 9 g/dl, platelet count $\geq 100{,}000/mm^3$, serum bilirubin < 1.25 times the upper limit of normal (ULN), AST or ALT < 2.5 times ULN (< 5.0 times ULN in the presence of liver metastases), serum creatinine ≤ 2.0 mg/dl or calculated creatinine clearance < 60 ml/min [17]. Patients were at least 18 years of age, had a WHO performance status less than 2, and a body surface area of at least 1.2 m^2. Their expected survival was at least 12 weeks. 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.

Patients had to have recovered from the acute effects of any prior therapy or have stable symptoms of grade 2 or less by Common Toxicity Criteria (CTC). They could not have brain metastases that required corticosteroid therapy or were progressive, symptomatic, or associated with edema by CT or MRI. They could not have had any chemotherapy, radiotherapy, surgery or other investigational drug within 4 weeks of the first treatment (6 weeks for prior nitrosoureas or mitomycin C). Patients with prostate or breast cancer were permitted to continue androgen suppression or antiestrogen therapy provided that they had been on that therapy for at least 3 months prior to enrollment. Patients could not have received radiation therapy to more than 30% of the bone marrow compartment or more than 6 months of chlorambucil, mitomycin C, or nitrosoureas within the previous 12 months. They could not have an active infection or significant medical problem which might limit their ability to receive treatment. Pregnant or breast-feeding women were also excluded.

Toxicity was graded using the CTC (version 2.0, Cancer Therapeutics Evaluation Program, National Cancer Institute). Dose-limiting toxicity (DLT) was defined as an ANC $< 500/mm^3$ for 5 or more days, platelet count $< 10{,}000/mm^3$, ANC $< 500/mm^3$ with fever requiring antibiotics, or nonhematologic toxicity of at least grade 3 using the CTC with the exception of transient, reversible transaminase elevations or nausea and vomiting in patients with suboptimal antiemetic therapy. A treatment delay of more than 3 weeks due to unresolved toxicity also constituted a DLT. The maximum tolerated dose (MTD) was defined as one dose level below the level that induced DLT in more than one-third of patients. The last patient enrolled to a given dose level was observed for at least 2 weeks prior to enrolling patients to a higher dose level.

It was intended to accrue three patients to each dose level. In the event of DLT in one of the three patients, provision was made to accrue an additional three patients to that dose level. If more than two patients experienced a DLT, then the MTD was determined. If two patients experienced DLT, accrual continued to that dose level to a total of six patients. If DLT occurred in two of six patients, subsequent patients were accrued to the next dose level. A 33% rate of DLT was considered acceptable given the rate of dose-limiting neutropenia and thrombocytopenia associated with gemcitabine when combined with standard platinum analogues, such as cisplatin and carboplatin. The doses of ZD0473 and gemcitabine were escalated according to a predetermined scheme (Table 1).

Prior to the initiation of therapy, each patient was evaluated with a history, physical examination, tumor measurement using an appropriate radiographic technique, assessment of WHO performance status, complete blood count with differential, serum chemistries, urinalysis and electrocardiogram. Each of these, with the exception of tumor measurement, was performed prior to the administration of each subsequent cycle. Complete blood counts and serum chemistries were performed weekly during the first cycle, with more frequent monitoring in the event of myelosuppression.

Table 1 Dose escalation scheme and chronological order of patient accrual

Dose level	No. of patients	ZD0473 (mg/m^2)	Gemcitabine (mg/m^2)
1	8	60	750
2	5	90	750
3	6	120	750
4[a]	12	90	750
5[b]	5	90	600

[a]Lightly pretreated
[b]Heavily pretreated

Patients received ZD0473 as a 1-h intravenous infusion on day 1 of each 21-day cycle. Gemcitabine was administered 30 min after completion of ZD0473 on day 1 and alone on day 8 by intravenous infusion over 30 min. Prior to receiving gemcitabine on day 8, or subsequent cycles, patients were required to have an ANC $\geq 1500/mm^3$, platelet count $\geq 100{,}000/mm^3$, and serum creatinine < 1.25 times ULN. The doses of ZD0473 and gemcitabine were reduced by 25% in the event of grade 4 hematologic toxicity or grade 3 or 4 nonhematologic toxicity. The dose of gemcitabine was reduced by 25% if the day-8 doses were held in two consecutive cycles.

Patients were evaluated for response after every other treatment cycle. 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 characteristics

Between January 2000 and May 2001, 36 patients were enrolled in this study. The last patient to be removed from the study continued to receive treatment through February 2002. The baseline characteristics of the patients are presented in Table 2. Lung and pancreas were the most common primary sites of cancer. The majority of patients had received prior chemotherapy; however 13 patients (36%) had not. WHO performance status was nearly equally divided between 0 and 1.

Dose escalation

The second and third patients accrued to the first dose level experienced DLT, grade 4 neutropenia lasting more than 5 days in one and grade 4 thrombocytopenia in the other. The sixth patient accrued to the first dose level progressed rapidly and only received treatment on day 1 of the first cycle. Therefore, a seventh patient was added. In the absence of any further DLT, subsequent patients were accrued to the second dose level. At the second dose level, no DLTs were observed in the first three patients. As this initial cohort had done well and the next dose level was not yet approved for accrual, two additional patients

Table 2 Patient characteristics

Total patients enrolled	36
Male	18
Female	18
Age (years)	
Median	57
Range	40–80
ECOG performance status	
0	19
1	17
Primary disease site	
Lung	14
Pancreas	6
Sarcoma	5
Ovary	3
Breast	2
Colon	2
Melanoma	2
Gastroesophageal junction	1
Appendix	1
Prior treatments	
Chemotherapy	15
None	13
Chemotherapy and radiation	4
Chemotherapy and surgery	3
Chemotherapy, surgery and radiation	1

were added to this level. The fifth patient experienced dose-limiting thrombocytopenia. The third patient on the third dose level experienced a DLT. Three patients were added to this level, one of whom experienced a DLT. Grade 3 or 4 hematologic toxicity occurred in four of the six patients at this level. This frequency and severity of toxicity precluded further dose escalation.

Through the first three dose levels it was observed that three of four instances of grade 4 thrombocytopenia occurred in heavily pretreated patients. One such patient had received numerous chemotherapy regimens including an autologous bone marrow transplant and the others had received prior platinum-based chemotherapy. Subsequent patients were stratified as lightly or heavily pretreated. Patients with at least two prior courses of myelosuppressive chemotherapy, or one prior myelosuppressive regimen together with radiation therapy to at least 30% of the bone marrow compartment, were considered heavily pretreated. In order to confirm the MTD, 12 lightly pretreated patients were accrued to the second dose level. As thrombocytopenia was known to be a common toxicity of gemcitabine, five heavily pretreated patients were accrued to a newly designated dose level with a reduced dose of gemcitabine (Table 1). One patient, in whom therapy at dose level five was intended, was treated with 60 mg/m^2 of ZD0473 and 600 mg/m^2 of gemcitabine for two cycles. For toxicity analyses he is included in the first dose level.

Toxicity

Hematologic toxicity was the most frequently observed severe toxicity (Tables 3 and 4). In the first cycle, grade 3 or 4 neutropenia and thrombocytopenia occurred with equal frequency (16 of 36 cycles, 44%).

Table 3 Hematologic toxicity—first cycle

Dose level (mg/m^2)	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
ZD0473 60, gemcitabine 750	8[a]	2	1	1	3	0	0	2	1	1
ZD0473 90, gemcitabine 750	5	2	2	0	2	1	0	1	2	1
ZD0473 120, gemcitabine 750	6	0	0	4	4	1	0	0	4	2
ZD0473 90, gemcitabine 750	12	1	1	3	2	1	0	5	1	1
ZD0473 90, gemcitabine 600	5	0	2	2	2	1	0	1	1	2
Totals	36	5	6	10	13	4	0	9	9	7

[a]Includes one patient treated at ZD0473 60 mg/m^2 and gemcitabine 600 mg/m^2

Table 4 Hematologic toxicity—all cycles

Dose level (mg/m^2)	Number of cycles	Number of events								
		Neutropenia			Anemia			Thrombocytopenia		
		Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
ZD0473 60, gemcitabine 750	36[a]	9	6	1	16	4	0	5	9	2
ZD0473 90, gemcitabine 750	24	7	8	2	10	5	1	3	14	2
ZD0473 120, gemcitabine 750	17	0	1	8	10	3	1	1	11	4
ZD0473 90, gemcitabine 750	42	1	6	5	16	10	0	16	17	1
ZD0473 90, gemcitabine 600	27	0	12	3	10	6	0	2	12	3
Totals	126	17	33	19	62	28	2	27	63	12

[a]Includes one patient treated at ZD0473 60 mg/m^{2}and gemcitabine 600 mg/m^2

Over all treatment cycles, severe thrombocytopenia complicated more cycles (60%) than severe neutropenia (41%). Grade 2 and 3 anemia were also common, occurring after 47% of first cycles and 71% of all cycles. There were two instances of grade 4 anemia.

Of the nonhematologic toxicities that were possibly or probably related to treatment, mild fatigue and nausea were most common. Dyspnea or peripheral edema complicated 22% of all cycles. Severe toxicities that were related to treatment included four instances of grade 3 or 4 fatigue, two cases of grade 3 dyspnea and one case of grade 3 peripheral edema. All other symptoms were infrequent and mild.

Of the laboratory abnormalities seen, mild and reversible liver enzyme elevations and hyperglycemia were the most common. There were ten instances of grade 3 elevation of AST or ALT. Four of these abnormalities had resolved to grade 1 or less by the next cycle, and the other six occurred in one patient with a baseline grade 2 elevation of both AST and ALT.

Responses

Of the 36 patients enrolled, 35 were evaluable for response. Two partial responses were observed in patients at the first dose level. One occurred in a 42-year-old woman with leiomyosarcoma who had received no prior chemotherapy. She was treated for 12 cycles prior to discontinuation for disease progression. A 53-year-old woman with ovarian cancer achieved a partial response and received seven cycles of therapy. She had received eight prior chemotherapy regimens, three of which were platinum-based.

Stable disease was seen in 19 patients. Nine of these patients had lung cancer and four had pancreatic cancer. The others were diagnosed with melanoma, appendix, leiomyosarcoma, gastrointestinal stromal, colon and gastroesophageal junction tumors. The median duration of treatment was 5 cycles and ranged from 3 to 20 cycles. The 62-year-old woman with colon cancer, who received 20 cycles of ZD0473 and gemcitabine, had progressive disease following 5-fluorouracil and leucovorin without, and then with, irinotecan, as well as oxaliplatin. Progressive disease occurred in 14 patients.

Discussion

We performed a dose-escalation study of ZD0473 and gemcitabine in order to determine the MTD of the combination. Using a 21-day treatment cycle, both drugs were administered on day 1 and gemcitabine was given alone on day 8. Based on hematologic DLTs at the third dose level, we identified 90 mg/m^2 of ZD0473 as the MTD when given in combination with gemcitabine. For lightly pretreated patients, 750 mg/m^2 of gemcitabine is the recommended dose, whereas for heavily pretreated patients, 600 mg/m^2 is recommended.

As with previous single-agent studies, thrombocytopenia was the predominant hematologic toxicity observed in our study. The frequency of grade 3 or 4 thrombocytopenia, neutropenia and anemia was higher with our combination compared to single-agent ZD0473. This is not surprising in light of the well-described myelosuppression associated with gemcitabine. A review of single-agent trials of gemcitabine found that rates of grade 3 and 4 neutropenia, anemia and thrombocytopenia were 25%, 8%, and 5%, respectively [18]. In this trial, patients with prior exposure to alkylating agents appeared to have a higher incidence of severe myelosuppression. For that reason, we evaluated two distinct recommended phase II dose levels, one for patients with minimal prior therapy and one for more heavily pretreated patients.

ZD0473 has been evaluated in two phase I clinical trials as a single agent. Trigo et al. reported the preliminary results of an ongoing dose escalation study among 22 patients with advanced cancers [6]. The dose of ZD0473 ranged from 12 to 130 mg/m^2 with a 21- or 28-day cycle length. Dose-limiting thrombocytopenia was seen in three of five patients at the highest level; grade 3 neutropenia was also seen in two patients. Pharmacokinetic studies revealed a linear relationship between dose and AUC of ZD0473, assayed by atomic absorption spectroscopy for platinum, at lower, but not higher, doses. There was no clear relationship between AUC and the incidence of thrombocytopenia ($r^2 = 0.55$). Elimination was triphasic with mean half-lives of 0.3, 2.3, and 73.7 h.

We performed a dose escalation study of single agent ZD0473 among 22 minimally pretreated patients with advanced cancers [7]. ZD0473 was administered intravenously on a 21-day cycle at doses ranging from 120 to 180 mg/m^2. Dose-limiting hematologic toxicity occurred in three of five patients at 180 mg/m^2, defining 150 mg/m^2 as the recommended phase II dose. No evidence of nephrotoxicity, ototoxicity or neurotoxicity was observed. Using a novel stable isotope dilution liquid chromatography, tandem mass spectrometry assay to determine drug concentration, we found that AUC increased linearly with dose increment in this range. There was a correlation between AUC and the severity of thrombocytopenia and a pharmacodynamic model was developed.

The preliminary results of six ongoing single-agent phase II clinical trials have been reported [19]. In each of these trials the dose of ZD0473 was escalated from 120 to 150 mg/m^2. Of 99 patients enrolled in those trials, grade 3 or 4 thrombocytopenia occurred in 40%, neutropenia in 28%, and anemia in 19%. Significant clinical activity was observed in the first-line treatment of mesothelioma [20] and as second-line for NSCLC [21], small-cell lung cancer [22], ovarian cancer [23], and breast cancer [24].

The MTD of ZD0473 alone is 150 mg/m^2. Thus the combination of ZD0473 and gemcitabine differs from cisplatin and gemcitabine in which a full dose of

cisplatin can be administered. At the recommended phase II doses, the toxicity associated with this combination is tolerable. The severity of myelosuppression appears to be related to prior treatment. With the reduced dose of gemcitabine (600 mg/m^2), the heavily pretreated patients continued to experience a high rate of grade 3 and 4 neutropenia and thrombocytopenia. Further studies of this combination will require careful monitoring of this subset of patients.

Clinical activity has been observed with ZD0473 alone and in combination. However, the rate of response does not clearly distinguish it from cisplatin and carboplatin. The activity seen in patients who had progressed despite therapy with platinum-containing regimens suggests some lack of cross-resistance with ZD0473, as seen in preclinical studies. The results of preclinical and early clinical studies provide a rationale for pursuing this combination in NSCLC, and pancreatic and bladder cancers.

In summary, we found that dose-dependent thrombocytopenia and neutropenia are dose-limiting with the combination of ZD0473 and gemcitabine. At the recommended phase II doses, hematologic toxicity was manageable. Nonhematologic toxicities were mild and reversible. Of note, significant nephrotoxicity, ototoxicity and neurotoxicity were not seen. Clinical activity was observed, with over half of patients demonstrating stable disease for at least three cycles. ZD0473, alone and in combination, is a broadly active agent. Further studies are needed to determine if it is superior to cisplatin and carboplatin.

References

1. Kelland LR (2000) Preclinical perspectives on platinum resistance. Drugs 59 [Suppl 4]:1–8
2. Hamilton TC, Winker MA, Louie KG, Batist G, Behrens BC, Tsuruo T, Grotzinger KR, McKoy WM, Young RC, Ozols RF (1985) Augmentation of adriamycin, melphalan, and cisplatin cytotoxicity in drug-resistant and -sensitive human ovarian carcinoma cell lines by buthionine sulfoximine mediated glutathione depletion. Biochem Pharmacol 34:2583–2586
3. Godwin AK, Meister A, O'Dwyer PJ, Huang CS, Hamilton TC, Anderson ME (1992) High resistance to cisplatin in human ovarian cancer cell lines is associated with marked increase of glutathione synthesis. Proc Natl Acad Sci U S A 89:3070–3074
4. Holford J, Raynaud F, Murrer BA, Grimaldi K, Hartley JA, Abrams M, Kelland LR (1998) Chemical, biochemical and pharmacological activity of the novel sterically hindered platinum co-ordination complex, cis-[amminedichloro(2-methylpyridine)] platinum(II) (AMD473). Anticancer Drug Des 13:1–18
5. Raynaud FI, Boxall FE, Goddard PM, Valenti M, Jones M, Murrer BA, Abrams M, Kelland LR (1997) cis-Amminedichloro(2-methylpyridine) platinum(II) (AMD473), a novel sterically hindered platinum complex: in vivo activity, toxicology, and pharmacokinetics in mice. Clin Cancer Res 3:2063–20674
6. Trigo JM, Beale P, Judson IR, Raynaud F, Rees C, Milan D, Wolf L, Walker R, Hanwell J, Giandomenico C (1999) Phase I and pharmacokinetic (PK) study of cis-amminedichloro (2-methylpyridine) platinum (II) (ZD0473), a novel sterically hindered platinum complex, in patients (pts) with advanced solid malignancies. Proc Am Soc Clin Oncol, abstract 648
7. Stevenson JP, Blair IA, Redlinger M, Sun W, Oe T, Garcia-Vargas J, Roberts DW, Oliver R, O'Dwyer PJ (2001) Pharmacokinetic/pharmacodynamic trial of the new generation platinum agent ZD0473 administered as an iv infusion every 21 days. Proceedings of the AACR-NCI-EORTC International Conference, abstract 710
8. Cormier Y, Eisenhauer E, Muldal A, et al (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]:S8–16
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. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH (2002) The Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–98
16. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kerbrat P, Sanchez Rovira P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Grul CM, Conte PF (2000) Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 18:3068–3077
17. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
18. Aapro MS, Martin C, Hatty S (1998) Gemcitabine—a safety review. Anticancer Drugs 9:191–201
19. Hoctin-Boes G, Cosaert J, Koehler M, Smith M (2001) Safety profile of ZD0473 in phase II trials of patients with advanced cancers. Proc Am Soc Clin Oncol, abstract 1372
20. Giaccone G, O'Brien M, Byrne MJ, Van Steenkiste J, Cosaert J (2001) Phase II trial of ZD0473 in patients with mesothelioma relapsing after one prior chemotherapy regimen. Proc Am Soc Clin Oncol, abstract 2781
21. Quoix E, Moro D, Cosaert J (2001) ZD0473 phase II monotherapy trial in first-line non-small cell lung cancer. Proc Am Soc Clin Oncol, abstract 2774
22. Bonomi P, Modiano M, Cornett P, Koehler M, Schiller J (2001) Phase II trial to assess the activity of ZD0473 in patients with small-cell lung cancer who have failed one prior platinum-based chemotherapy regimen. Proc Am Soc Clin Oncol, abstract 1284
23. Gore M, Atkinson RJ, Dirix L, Rischin D, Beale P, Harnet P, Hacking D, Cure H, Cosaert J (2001) ZD0473 phase II monotherapy trial in second-line ovarian cancer. Proc Am Soc Clin Oncol, abstract 2501
24. Vandenberg TA, Gelmon KA, Panasci L, Crump M, Norris B, Tomiak A, Shenkier T, Lee CW, Martin LA, Matthews S, Seymour LK, Douglas L (2001) Phase II trial of ZD0473 in patients with metastatic breast cancer. A National Cancer Institute of Canada Clinical Trials Group Study (NCIC CTG-IND 129). Proc Am Soc Clin Oncol, abstract 1981