Cancer Chemother Pharmacol (2005) 55: 559–564
DOI 10.1007/s00280-004-0916-9

ORIGINAL ARTICLE

Henry Q. Xiong · William Plunkett · Robert Wolff
Min Du · Renato Lenzi · James L. Abbruzzese

A pharmacological study of celecoxib and gemcitabine in patients with advanced pancreatic cancer

Received: 11 February 2004 / Accepted: 1 September 2004 / Published online: 22 February 2005

Abstract *Purpose*: To evaluate whether celecoxib alters the conversion of gemcitabine into its active metabolite, difluorodeoxycytidine triphosphate (dFdCTP), in peripheral blood mononuclear cells (PBMCs). *Methods*: Patients with advanced pancreatic cancer who had not received chemotherapy and had acceptable organ function were eligible for the study. The initial dose of gemcitabine was 750 mg/m^2 administered intravenously at a rate of 10 mg/m^2/min on days 1, 8, and 15 every 4 weeks. Celecoxib was administered orally at 400 mg twice a day starting 2 days after the first dose of gemcitabine. Serial blood samples were taken during the first and second gemcitabine infusions and the cellular dFdCTP levels from PBMCs were analyzed. *Results*: Five patients received gemcitabine at 750 mg/m^2 and six patients received it at 650 mg/m^2. Severe adverse events included neutropenia, thrombocytopenia, enteritis, and gastric perforation. Two patient died early during treatment. Cellular pharmacology studies showed that the conversion of gemcitabine into dFdCTP was not affected by celecoxib. *Conclusion*: Despite the increased clinical toxicities encountered with the combination, celecoxib did not alter the conversion of gemcitabine into its active metabolites in PBMCs. Gemcitabine 650 mg/m^2 infusion over 65 min on days 1, 8, and 15 every 4 weeks in combination with celecoxib at 400 mg twice a day was the dose recommended for further study.

H. Q. Xiong (✉) · R. Wolff · R. Lenzi · J. L. Abbruzzese
Department of Gastrointestinal Medical Oncology,
Unit 426, The University of Texas M. D. Anderson Cancer Center,
1515 Holcombe Boulevard, Houston, TX 77030, USA
E-mail: qxiong@mailmdanderson.org
Tel.: +1-713-7922828
Fax: +1-713-7451163

W. Plunkett · M. Du
Department of Experimental Therapeutics, Unit 71,
The University of Texas M. D. Anderson Cancer Center,
Houston, TX 77030, USA

Keywords Pancreatic cancer · Celecoxib · Gemcitabine · Cellular pharmacology

Introduction

Gemcitabine is a prodrug that must be phosphorylated to its active metabolites, difluorodeoxycytidine diphosphate and difluorodeoxycytidine triphosphate (dFdCTP), to have biological activity. Preclinical and clinical studies demonstrated that accumulation of dFdCTP in mononuclear cells is both dose- and infusion rate-dependent [1–3]. The rate of dFdCTP accumulation and the peak cellular concentration are highest at an infusion rate of 10 mg/m^2/min. No further increase of dFdCTP in mononuclear cells is observed as the dose of gemcitabine increases, suggesting that the ability of mononuclear cells to convert gemcitabine to dFdCTP is saturable. Therefore, gemcitabine administered at 10 mg/m^2/min results in a higher intracellular level of dFdCTP than the level achieved when gemcitabine is infused over 30 min.

Gemcitabine is an approved chemotherapy for advanced pancreatic cancer. It offers clinical benefit and marginal survival advantage to patients with advanced pancreatic cancer [4]. However, the median survival duration in patients with metastatic pancreatic cancer continues to be less than 6 months. Study of novel targets and strategies is greatly needed to improve the treatment outcome in patients with this disease.

Overexpression of cyclooxygenase 2 (COX-2) has been observed in more than 75% of invasive ductal carcinomas, suggesting that COX-2 may be involved in pancreatic tumorigenesis [5–11]. Nonsteroidal antiinflammatory drugs (NSAIDs), such as aspirin and indomethacin, have long demonstrated anticancer effects in rodents. Recently, a clinical trial of celecoxib in patients with familial adenomatous polyposis has demonstrated that a selective COX-2 inhibitor, celecoxib, at a dose of 400 mg orally twice a day, reduces the number of

colorectal polyps by 28% [12]. This study also demonstrated that celecoxib at 400 mg orally twice a day has biological activity in reducing the size of colonic polyps, and therefore this dose has been used in many subsequent clinical trials for cancer prevention and treatment.

NSAIDs and selective COX-2 inhibitors have demonstrated activity against pancreatic cancer through cell cycle arrest, induction of apoptosis, and antiangiogenesis [10, 13–16]. The combination of COX inhibitors with gemcitabine has demonstrated additive activity against pancreatic cancer in preclinical settings [13, 14]. Thus, it was considered reasonable to explore the combination of celecoxib with gemcitabine in the treatment of pancreatic cancer. Since gemcitabine is a prodrug whose metabolism could be potentially affected by concurrent medications and there were no clinical data on the potential interaction and toxicity between these two drugs, we conducted a phase I study to determine if celecoxib alters the metabolism of gemcitabine and to evaluate the toxicity of the combination.

Patients and methods

Patient eligibility

Patients were eligible for the trial if they had histologically or cytologically confirmed metastatic or locally advanced unresectable pancreatic cancer, age ≥18 years, life expectancy > 12 weeks, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, leukocytes ≥3000/μl, an absolute neutrophil count ≥1500/μl, platelets ≥100,000/μl, total bilirubin within the institutional upper limit of normal, aspartate aminotransferase/alanine aminotransferase not more than 2.5 times the institutional upper limit of normal, and creatinine ≤ 1.5 mg/dl. Patients were excluded if they had a history of radiotherapy within the previous 4 weeks, prior chemotherapy for metastatic pancreatic cancer, concomitant therapy with any other investigational agents, known brain metastases, on-going use of NSAIDs for any reason, known gastric or duodenal ulcer, allergic reactions attributed to compounds of similar chemical or biologic composition to celecoxib or to sulfonamides.

Treatment

The treatment plan consisted of enrollment of six patients at each dose level to ensure sufficient sample size for cellular pharmacokinetic analysis and evaluation of toxicity. Gemcitabine was administered at a dose of 10 mg/m^2/min days 1, 8, 15 every 4 weeks. The starting dose of gemcitabine was 750 mg/m^2 with a plan to escalate to 1000 mg/m^2 if there were no dose-limiting toxicity (DLT) or decrease to 650 mg/m^2 if DLTs occurred. If a patient grade 3 or worse neutropenia or thrombocytopenia or grade 2 or worse nonhematological toxicities on the day of scheduled treatment, the gemcitabine was held until resolution of toxicity to grade 1 or less. If patients developed toxicity requiring omission of week 2 or week 3 treatment during the previous cycle, the gemcitabine dose was reduced by 25% for the next cycle.

Celecoxib was administered orally at 400 mg twice a day starting 2 days after the first dose of gemcitabine. There was no dose modification for celecoxib. Patients were taken off study for adverse events that were related to celecoxib and required its discontinuation.

Assessment of toxicity and response

Adverse events were graded using the National Cancer Institute (NCI) Common Toxicity Criteria version 2.0. DLTs were defined as follows: grade 3 or worse nonhematological toxicity (excluding nausea or vomiting), grade 3 or worse nausea or vomiting uncontrolled by aggressive antiemetic support, grade 4 neutropenia lasting 3 days or longer without the use of filgrastim, fever of 38.5°C or more with grade 3 or worse neutropenia of any duration, grade 4 thrombocytopenia, grade 3 or worse neutropenia or thrombocytopenia on a treatment day, or a grade 2 nonhematological toxicity that, in the judgment of the investigator, required a decrease in dose.

Patients underwent imaging studies every 8 weeks for assessment of antitumor activity. Response and progression were evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee [17].

Pharmacokinetics

Blood samples were obtained at time 0 (before gemcitabine infusion), and then 25, 50, 75, and 100 min after the infusion started during the first dose of gemcitabine (without celecoxib) and second dose of gemcitabine (with celecoxib). The blood samples were centrifuged for 10 min at 5000 rpm to remove plasma. The cell pellet was resuspended in 40 ml phosphate-buffered saline (PBS) and layered over 10 ml Ficoll-Hypaque mixture (specific gravity, 1.077 g/ml). After centrifugation at 400 *g* at 4°C for 20 min, the buoyant mononuclear cells were removed and diluted to 10 ml with PBS. dFdCTP was assayed using anion exchange high-pressure chromatography, as previously described [18, 19].

Results

Patient characteristics

A total of 12 patients were enrolled in the study. One patient withdrew consent before receiving the treatment and therefore was inevaluable. Five patients received gemcitabine at 750 mg/m^2, and six patients received it at

Table 1 Patient characteristics

Number of patients[a]	11
Age (years)	
Median	65
Range	34–70
Sex (female/male)	6/5
Performance status	
0	2
1	9
Metastatic disease	10
Prior therapy	
None	6
Chemoradiation	2
Surgery	5

[a]Twelve patients were enrolled; one patient withdrew consent before treatment

650 mg/m^2. Table 1 summarizes the characteristics of these patients. Of the 11 treated patients, 10 had metastatic disease. Two patients developed metastatic disease after surgical resection of the primary pancreatic cancer followed by adjuvant chemoradiation.

Toxicities

Table 2 shows the clinically relevant adverse events for patients treated with gemcitabine and celecoxib. All severe adverse events were observed during cycle 1. The starting dose of gemcitabine was 750 mg/m^2. Two DLTs were observed at this dose level: one patient developed a grade 3 skin rash, and another patient died 1 week after the treatment. The patient died during sleep, and the cause of death was unknown but presumed to be a cardiovascular or thrombotic event.

We were unable to escalate the dose of gemcitabine to 1000 mg/m^2 as planned and instead had to reduce it to 650 mg/m^2 because of two DLTs at the previous dose level. Two DLTs were observed at this dose level. One patient developed grade 4 neutropenia and perforation of a gastric ulcer following two doses of gemcitabine and daily celecoxib. The patient subsequently died of complications of gastric perforation. An autopsy was performed, which confirmed the presence of the gastric ulcer with perforation and underlying tumor invasion. The second patient developed grade 3 enteritis after two doses of gemcitabine and was taken off study.

Significant hematologic toxicity was also encountered. Of the patients in the first cohort who received 750 mg/m^2 gemcitabine, two patients developed grade 3 neutropenia and one patient had grade 3 thrombocytopenia, whereas one patient developed grade 4 neutropenia and two patients developed grade 3 thrombocytopenia at the 650 mg/m^2 dose. Other common grade 1 and 2 adverse events throughout all cycles of treatment included nausea (nine), fatigue (eight), anorexia (seven), vomiting (five), and diarrhea (two). Additionally, two patients had grade 3 abdominal pain and one patient had grade 3 vomiting.

One patient required dose reduction after cycle 1 at a dose level of 650 mg/m^2, whereas two patients required dose reduction after cycles 3 and 4 and again after cycles 4 and 6 when gemcitabine was started at 750 mg/m^2, respectively.

Efficacy

Tumor response was initially evaluated 2 months after treatment in five patients. One patient had a partial response and four patients had stable disease at initial assessment. One patient withdrew consent after one cycle and continued the same treatment closer to home for more than a year. The assessment of efficacy was hampered because of two early deaths and two DLTs that required discontinuation of therapy.

Gemcitabine triphosphate accumulation

The primary objective of the study was to evaluate whether celecoxib alters the metabolism of gemcita-

Table 2 Clinically relevant toxicities (number of patients experiencing specific toxicities during cycle 1)

	Gemcitabine dose levels (mg/m^2)							
	750 (five patients)				650 (six patients)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Abdominal pain	0	0	0	0	1	0	2	0
Anorexia	2	0	0	0	3	0	0	0
Diarrhea	0	1	0	0	1	0	0	0
Edema	0	1	0	0	0	0	0	0
Fatigue	4	1	0	0	1	1	0	0
Nausea	3	1	0	0	1	3	1	0
Skin rash	1	0	1	0	0	1	0	0
Enteritis	0	0	0	0	0	0	1	0
Gastric perforation[a]	0	0	0	0	0	0	0	1
Neutropenia	0	2	2	0	1	1	0	1
Thrombocytopenia	0	2	1	0	0	1	2	0
Anemia	2	1	0	0	2	1	0	0

[a]Gastric ulcer with perforation and underlying tumor. Patient died

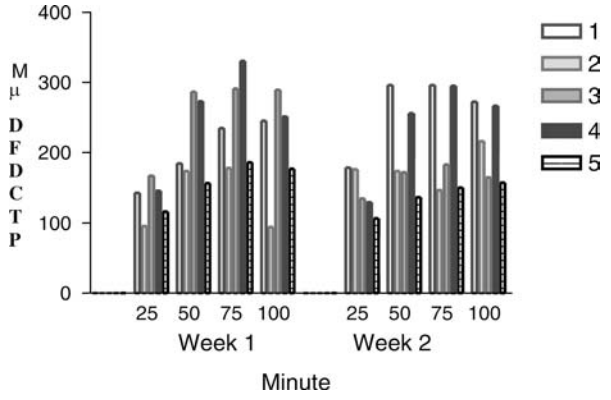

Fig. 1 dFdCTP concentrations in PBMCs at different time-points during gemcitabine infusion without celecoxib (week 1) and with celecoxib (week 2) administered at a dose of 650 mg/m^2 over 65 min (10 mg/m^2/min). Five patients (each bar represents a patient) had paired serial blood samples before beginning gemcitabine, and then at 25, 50, 75, and 100 min during and after gemcitabine infusion

bine. dFdCTP concentrations were detected in peripheral blood mononuclear cells (PBMCs) following gemcitabine (first dose) and gemcitabine plus celecoxib (second dose). Five patients from the second cohort (650 mg/m^2 gemcitabine) had paired serial blood samples. As expected, there was a linear increase in dFdCTP levels during the gemcitabine infusions in the majority of patients, as demonstrated in Fig. 1. The peak concentration of dFdCTP was at 75 min for most patients at gemcitabine 650 mg/m^2 (Table 3). Comparison of dFdCTP peak levels in paired PBMC samples revealed no significant difference ($P = 0.16$), indicating that celecoxib had no effect on the conversion of gemcitabine into its active metabolite, dFdCTP. Two patients from the first cohort (gemcitabine 750 mg/m^2) had complete paired serial blood samples for analysis of dFdCTP; the other three patients did not have serial blood samples for the second dose of gemcitabine (one early death, one taken off study due to grade 3 skin rash, and one did not receive gemcitabine at 10 mg/m^2/min; Table 3).

Table 3 DFdCTP peak levels (μM) after gemcitabine infusion

	750 mg/m^2		650 mg/m^2	
	Week 1	Week 2	Week 1	Week 2
	313	410	186	150
	313	238	331	295
	211		291	183
	318		178	146
			235	296
Median	289	324	203	198
P value[a]	N/A[b]		0.16	

[a]Student's *t*-test
[b]Not analyzed due to small sample size at week 2

Discussion

The high frequency with which celecoxib's molecular target, COX-2, is expressed in pancreatic cancer stimulated efforts to develop the combination of celecoxib and gemcitabine as a potential treatment for pancreatic cancer. In addition, celecoxib inhibits tumor growth through its effects on cell cycle progression, apoptosis, and angiogenesis. These effects are mechanistically distinct from those of gemcitabine, an anticancer agent that interferes with DNA and RNA synthesis. Since gemcitabine is a prodrug and there was no prior experience with the combination of these two agents, we conducted a phase I trial to evaluate the effect of celecoxib on the cellular pharmacology of gemcitabine, and also to evaluate toxicities and tolerability. The data obtained suggested that celecoxib did not substantially alter the metabolism of gemcitabine when gemcitabine was administered at a dose of 650 mg/m^2 at a fixed-dose rate of 10 mg/m^2/min. However, the limited dosing and small number of patients treated on this trial do not allow us to conclude that celecoxib does not alter gemcitabine cellular pharmacology when gemcitabine is administered at other doses or over shorter or longer infusion times.

Although unexpected, we observed significant adverse events in this study. There were two early deaths. At least one of the early deaths was clearly related to treatment since the patient died as a result of a perforated gastric ulcer with associated tumor involvement and concurrent neutropenia. Moreover, several episodes of significant neutropenia and thrombocytopenia were observed during the first cycle of treatment. The incidence of neutropenia and thrombocytopenia seemed more frequent than one would anticipate from our experience with gemcitabine monotherapy. This might simply be explained by chance since the sample size was small. Alternatively, the high incidence of myelosuppression could have been related to the addition of celecoxib. While the mechanism whereby celecoxib might enhance chemotherapy-induced myelosuppression remains unknown, a preclinical study indicated that COX-2 induction is an important event in accelerated hematopoiesis following cytotoxic injury and that blocking COX-2 activity delays bone marrow recovery [20]. An increased frequency of neutropenia was observed in another study in which celecoxib was combined with carboplatin and paclitaxel [21].

In this trial, administration of gemcitabine at a fixed dose rate might also have contributed to the increased myelosuppression [22]. The widely accepted approach to the administration of gemcitabine involves weekly dosing at 1000 mg/m^2 over 30 min. Much higher doses of gemcitabine administered at a fixed dose rate of 10 mg/m^2/min have been used in several clinical trials. Touroutoglou et al. [3] conducted a phase I trial of gemcitabine administered weekly at a fixed dose rate of 10 mg/m^2/min and

recommended 1500 mg/m^2/min for further trials. Tempero et al. [22] subsequently compared gemcitabine 1500 mg/m^2 administered at a fixed dose rate of 10 mg/m^2/min with gemcitabine 2200 mg/m^2 administered over 30 min in patients with advanced pancreatic cancer. In that study, approximately 25% of the patients on the fixed dose rate regimen required either dose reduction or omission due to myelosuppression, but significant antitumor activity was observed.

In this study, we reported the lowest maximum tolerated dose (MTD) of gemcitabine was 650 mg/m^2 when administered at a fixed dose rate of 10 mg/m^2/min in combination with celecoxib. This substantial reduction in MTD may have been due to the different DLT criteria used in this study. Traditionally, DLTs have been commonly defined as occurrences of severe toxicities felt to be caused by the investigational treatment. However, it can be difficult to determine the causal relationship. Investigators and regulatory agencies have increasingly begun to define DLT as any serious adverse event, regardless of its relationship to the investigational treatment, and this definition was used in this study. In our study, the gemcitabine starting dose was 750 mg/m^2, and we initially intended to escalate it to 1000 mg/m^2. Instead, a dose reduction of gemcitabine was required due to the occurrence of two DLTs observed at the 750 mg/m^2 dose. One patient experienced a grade 3 skin rash and another patient died of unknown etiology, presumably due to a cardiac or thromboembolic event. Neither of these events would be considered DLTs according to more commonly used DLT criteria since these events were not considered to be dose-related or drug-related. Nevertheless, we did observe dose-related toxicities, including grade 3 enteritis and gastric perforation with concurrent neutropenia, when patients received gemcitabine at 650 mg/m^2, indicating that this dose was sufficient. The dose-related adverse events observed at gemcitabine 650 mg/m^2 raised the concern as to whether lower doses of gemcitabine should be studied. Since several studies have demonstrated that gemcitabine could be administered at much higher doses and in combination with other cytotoxic agents, we elected not to pursue lower dose levels of gemcitabine. The toxicity of this regimen would be further evaluated in a phase II study. The rationale for this decision was based on our impression that the true tolerability of this regimen could be best assessed in a larger phase II experience. The lower doses of gemcitabine were not studied due to concern for reduced efficacy, although systemic antitumor activity of gemcitabine was observed at lower doses (400 mg/m^2) in another study [23].

In conclusion, celecoxib does not appear to alter the cellular metabolism of gemcitabine. The MTD of gemcitabine is 650 mg/m^2 given as a 65-min infusion in combination with 400 mg of celecoxib twice a day. A phase II trial is currently underway to examine the efficacy of this combination in patients with advanced pancreatic cancer.

Acknowledgements The study was funded in part by a research grant from Pfizer. The authors thank Pamela Dumas for excellent research nursing support and Gail Bland for administrative support and editorial comments.

References

1. Grunewald R, Kantarjian H, Keating MJ, Abbruzzese J, Tarassoff P, Plunkett W (1990) Pharmacologically directed design of the dose rate and schedule of 2′,2′-difluorodeoxycytidine (gemcitabine) administration in leukemia. Cancer Res 50(21):6823–6826
2. Grunewald R, Abbruzzese JL, Tarassoff P, Plunkett W (1991) Saturation of 2′,2′-difluorodeoxycytidine 5′-triphosphate accumulation by mononuclear cells during a phase I trial of gemcitabine. Cancer Chemother Pharmacol 27(4):258–262
3. Touroutoglou N, Gravel D, Raber MN, Plunkett W, Abbruzzese JL (1998) Clinical results of a pharmacodynamically-based strategy for higher dosing of gemcitabine in patients with solid tumors. Ann Oncol 9(9):1003–1008
4. Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15(6):2403–2413
5. Kokawa A, Kondo H, Gotoda T, Ono H, Saito D, Nakadaira S, Kosuge T, Yoshida S (2001) Increased expression of cyclooxygenase-2 in human pancreatic neoplasms and potential for chemoprevention by cyclooxygenase inhibitors. Cancer 91:333–338
6. Koshiba T, Hosotani R, Miyamoto Y, Wada M, Lee JU, Fujimoto K, Tsuji S, Nakajima S, Doi R, Imamura M (1999) Immunohistochemical analysis of cyclooxygenase-2 expression in pancreatic tumors. Int J Pancreatol 26:69–76
7. Merati K, said Siadaty M, Andea A, Sarkar F, Ben-Josef E, Mohammed R, Philip P, Shields AF, Vaitkevicius V, Grignon DJ, Adsay NV (2001) Expression of inflammatory modulator COX-2 in pancreatic ductal adenocarcinoma and its relationship to pathologic and clinical parameters. Am J Clin Oncol 24:447–452
8. Okami J, Yamamoto H, Fujiwara Y, Tsujie M, Kondo M, Noura S, Oshima S, Nagano H, Dono K, Umeshita K, Ishikawa O, Sakon M, Matsuura N, Nakamori S, Monden M (1999) Overexpression of cyclooxygenase-2 in carcinoma of the pancreas. Clin Cancer Res 5:2018–2024
9. Tucker ON, Dannenberg AJ, Yang EK, Zhang F, Teng L, Daly JM, Soslow RA, Masferrer JL, Woerner BM, Koki AT, Fahey TJ III (1999) Cyclooxygenase-2 expression is upregulated in human pancreatic cancer. Cancer Res 59:987–990
10. Yip-Schneider MT, Barnard DS, Billings SD, Cheng L, Heilman DK, Lin A, Marshall SJ, Crowell PL, Marshall MS, Sweeney CJ (2000) Cyclooxygenase-2 expression in human pancreatic adenocarcinomas. Carcinogenesis 21:139–146
11. Maitra A, Ashfaq R, Gunn CR, Rahman A, Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Wilentz RE (2002) Cyclooxygenase 2 expression in pancreatic adenocarcinoma and pancreatic intraepithelial neoplasia: an immunohistochemical analysis with automated cellular imaging. Am J Clin Pathol 118(2):194–201
12. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, Wakabayashi N, Saunders B, Shen Y, Fujimura T, Su LK, Levin B (2000) The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 342(26):1946–1952
13. Molina MA, Sitja-Arnau M, Lemoine MG, Frazier ML, Sinicrope FA (1999) Increased cyclooxygenase-2 expression in human pancreatic carcinomas and cell lines: growth inhibition by nonsteroidal anti-inflammatory drugs. Cancer Res 59:4356–4362

14. Yip-Schneider MT, Sweeney CJ, Jung SH, Crowell PL, Marshall MS (2001) Cell cycle effects of nonsteroidal anti-inflammatory drugs and enhanced growth inhibition in combination with gemcitabine in pancreatic carcinoma cells. J Pharmacol Exp Ther 298(3):976–985
15. Masferrer JL, Leahy KM, Koki AT, Zweifel BS, Settle SL, Woerner BM, Edwards DA, Flickinger AG, Moore RJ, Seibert K (2000) Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. Cancer Res 60(5):1306–1311
16. Leahy KM, Ornberg RL, Wang Y, Zweifel BS, Koki AT, Masferrer JL (2002) Cyclooxygenase-2 inhibition by celecoxib reduces proliferation and induces apoptosis in angiogenic endothelial cells in vivo. Cancer Res 62(3):625–631
17. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumours. J Natl Cancer Inst 92:205–216
18. Plunkett W, Hug V, Keating MJ, Chubb S (1980) Quantitation of 1-b-D-arabinofuranosylcytosine 5′- triphosphate in the leukemic cells from bone marrow and peripheral blood of patients receiving 1-β-D-arabinofuranosylcytosine therapy. Cancer Res 40:588–591
19. Gandhi V, Plunkett W (1990) Modulatory activity of 2′,2′-difluorodeoxycytidine on the phosphorylation and cytotoxicity of arabinosyl nucleosides. Cancer Res 50:3675–3680
20. Lorenz M, Slaughter HS, Wescott DM, Carter SI, Schnyder B, Dinchuk JE, Car BD (1999) Cyclooxygenase-2 is essential for normal recovery from 5-fluorouracil-induced myelotoxicity in mice. Exp Hematol 27:1494–1502
21. Altorki NK, Keresztes RS, Port JL, Libby DM, Korst RJ, Flieder DB, Ferrara CA, Yankelevitz DF, Subbaramaiah K, Pasmantier MW, Dannenberg AJ (2003) Celecoxib, a selective cyclo-oxygenase-2 inhibitor, enhances the response to preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer. J Clin Oncol 21(14):2645–2650
22. Tempero M, Plunkett W, Ruiz Van Haperen V, Hainsworth J, Hochster H, Lenzi R, Abbruzzese JL (2003) Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21(18):3402–3408
23. Wolff RA, Evans DB, Gravel DM, Lenzi R, Pisters PW, Lee JE, Janjan NA, Charnsangavej C, Abbruzzese JL (2001) Phase I trial of gemcitabine combined with radiation for the treatment of locally advanced pancreatic adenocarcinoma. Clin Cancer Res 7(8):2246–2253