Pilot Study of Celecoxib and Infusional 5-Fluorouracil as Second-Line Treatment for Advanced Pancreatic Carcinoma

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BACKGROUND. Cyclooxygenase-2 (COX-2) is up-regulated frequently and may constitute a promising therapeutic target in patients with pancreatic ductal adenocarcinoma (PDAC).

METHODS. Patients with advanced PDAC who had progressive disease after gemcitabine-based chemotherapy were eligible for this pilot study. Treatment was comprised of oral celecoxib (400 mg twice daily) and protracted intravenous (i.v.) infusion 5-fluorouracil (5-FU) (200 mg/m^2 per day), both given continuously for a maximum of 9 treatment months, in the absence of disease progression or unacceptable toxicity. Patients were examined weekly for toxicity and were restaged every 6–8 weeks for tumor assessment.

RESULTS. Seventeen patients entered the study. Asymptomatic transaminase elevation was the most common toxicity and reached NCI-CTC (version 3.0) Grade 3–4 in 4 of 133 treatment weeks. No other hematologic or nonhematologic toxicity $>$ Grade 2 was observed. Four patients discontinued celecoxib due to upper gastrointestinal tract toxicity. Two confirmed partial responses (durations of 23 weeks and 68 weeks, respectively) and 2 patients with stable disease (durations of 10 weeks and 13 weeks, respectively) were observed for an overall response rate of 12% (95% confidence interval, 0–27%) in the intent-to-treat population. A significant decrease ($\geq$ 50%) in serum CA 19.9 levels was observed in 3 of 9 evaluable patients. The median time to disease progression was 8 weeks, and the median overall survival was 15 weeks.

CONCLUSIONS. The combination of oral celecoxib and 5-FU by protracted i.v. infusion was found to be feasible and well tolerated, and was capable of inducing durable objective responses, even in patients with far advanced, gemcitabine-resistant/refractory PDAC. Further exploration of COX-2 inhibitor/fluropyrimidine combinations is warranted. ***Cancer*** **2004;101:133–8.**

KEYWORDS: celecoxib, cyclooxygenase-2, infusional 5-fluorouracil, pancreatic carcinoma.

Mounting evidence suggests that cyclooxygenase-2 (COX-2), an inducible enzyme that catalyses the synthesis of prostaglandins, may represent an attractive pharmacologic target for inhibiting tumor growth. Indeed, increased levels of COX-2, compared with the levels in normal tissue, have been observed in a variety of malignancies.[1–4] The main product of COX-2, prostaglandin E_2, exerts pleiotropic effects both at the tumor cell level (promotion of cell growth, survival, and chemoresistance) and at the tumor-host interface (promotion of neoangiogenesis and immune suppression)[4,5]; moreover, the recently demonstrated ability of prostaglandin E_2 to transactivate the epider-

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mal growth factor receptor (EGFR)[6] makes therapeutic COX-2 targeting especially interesting for malignancies in which it is believed the EGFR pathway plays a relevant pathogenetic role. Although epidemiologic evidence of a protective effect of nonselective COX inhibitors (such as aspirin) on the incidence of pancreatic ductal adenocarcinoma (PDAC) is controversial, with several studies reporting either decreased risk[7,8] or increased risk[9,10] with increasing aspirin usage, several lines of evidence indicate that selective COX-2 inhibition, at least theoretically, may be of therapeutic benefit in patients with PDAC. First, COX-2 is up-regulated strongly in PDAC compared with normal pancreatic tissue or benign pancreatic lesions.[11–13]. Second, it has been shown that COX-2 blockade by selective pharmacologic inhibitors reduces in vitro cell growth in preclinical models of PDAC[14,15]. Third, COX-2 inhibitors exert synergistic proapoptotic and antitumor effects when combined with either gemcitabine or 5-fluorouracil (5-FU), the two drugs that currently constitute the mainstay of clinical PDAC treatment.[16,17] Altogether, these data provide a strong rationale for exploring COX-2 inhibitor-containing regimens in patients with advanced PDAC.

Until the introduction of gemcitabine, 5-FU was the cornerstone of chemotherapy for pancreatic carcinoma, even though there was no clear evidence of its benefit in patients with advanced disease.[18,19] Although earlier, 5-FU-based, multiagent regimens were reported to convey a survival advantage over best supportive care in patients with advanced PDAC,[20–22] such regimens were found to have increased toxicity without any survival benefit over single-agent 5-FU.[23] Given the short half-life ($t_{1/2}$) of 5-FU ($t_{1/2}$, 5–20 minutes), continuous intravenous (i.v.) infusion schedules have been devised to maximize tumor cell exposure to the drug, thereby increasing its activity. This approach has resulted in greater antitumor activity and better toxicity profiles compared with bolus administration in patients with colorectal carcinoma[24,25] and is being explored actively in other malignancies, including pancreatic carcinoma.[26–29] In the current study, we explored the feasibility and preliminary activity of a combination regimen comprised of celecoxib, an oral, selective COX-2 inhibitor, and protracted i.v. infusion (PIVI) 5-FU as second-line treatment in patients with advanced, inoperable PDAC.

MATERIALS AND METHODS

Patients age $\geq$ 18 years with a histologic or cytologic diagnosis of inoperable (locally advanced or metastatic) PDAC and confirmed progressive disease (PD) after first-line chemotherapy were eligible for this pilot trial. Additional eligibility criteria included the presence of measurable and/or evaluable disease; adequate hematologic, cardiovascular, renal, and hepatic function; and the use of an adequate contraception method for women of childbearing potential. Patients with unstable cardiovascular disease, active infections, documented active gastric/duodenal ulcer, or known or suspected allergy to sulfa drugs were considered ineligible. The protocol was reviewed and approved by the institutional ethical committee, and informed consent was obtained from all patients.

Treatment was comprised of oral celecoxib (400 mg twice daily) in combination with PIVI 5-FU (200 mg/m^2 per day), both given continuously, without scheduled interruptions, from Day 1 until disease progression or unacceptable toxicity, for a maximum of 9 treatment months. 5-FU was administered by a portable, elastomeric infusion pump (Surefuser®; Nipro Medical Corporation, Miami, FL) through a permanent central venous access device (Port-a-Cath®; Deltec, St. Paul, MN). The primary endpoint of the study was feasibility. The study was designed to reject the proposed treatment in the event of an incidence of severe toxicity (NCI-CTC Grade 3–4, version 3.0) $>$ 10%. To exclude an incidence of Grade 3 or 4 toxicity $>$ 10% reliably within a 95% confidence interval (95% CI), $<$ 7 severe adverse events were to be observed out of a total of 120 treatment weeks evaluable for toxicity. To this purpose, patients were monitored by weekly assessment of history and physical examination, complete blood cell counts and serum transaminase levels, and monthly assessment of complete serum chemistries. Temporary 5-FU interruption or 25% dose reductions were allowed in the event of toxicities $\geq$ Grade 3. Celecoxib discontinuation and/or dose reduction without 5-FU interruption were allowed in the event that, in the judgment of the investigators, a particular toxicity was deemed likely to be the result of celecoxib. In patients with elevated levels at baseline, serum CA 19.9 was monitored serially every 4 weeks. Activity was not a primary endpoint of the study; however, response to treatment was evaluated every 6–8 weeks, recorded according to standard World Health Organization criteria,[30] and confirmed at $\geq$ 4 weeks in the event of a complete response or a partial response (PR). The time to disease progression was calculated from the date of the initiation of treatment to the date of the first documentation of PD. Overall survival (OS) was calculated from the date of treatment initiation to the date of death or last follow-up.

RESULTS

Between September 2002 and September 2003, 17 patients (11 males and 6 females) were enrolled into this

TABLE 1
Patient Characteristics

Characteristic	No. of patients
Eligible patients	17
Male	11
Female	6
Age (yrs)	
Median	60
Range	35–68
Disease status	
Locally advanced	3
Metastatic	14
ECOG performance status	
0	6
1	10
2	1
Gemcitabine-pretreated patients	17
Single-agent gemcitabine	15
CDDP and gemcitabine	1
MTA and gemcitabine	1

ECOG: Eastern Cooperative Oncology Group; CDDP: cisplatin; MTA: multitarget antifolate.

TABLE 2
Hematologic and Nonhematologic Toxicity (National Cancer Institute Common Toxicity Criteria, version 3.0)

	No. (%)			
Toxicity[a]	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	5 (3.8)	—	—	—
Neutropenia	4 (3.0)	—	—	—
Thrombocytopenia	2 (1.5)	—	—	—
Anemia	9 (6.8)	4 (3.0)	—	—
AST	6 (4.5)	4 (3.0)	1 (0.8)	1 (0.8)
ALT	7 (5.3)	5 (4.5)	2 (1.5)	—
Diarrhea	3 (2.2)	1 (0.8)	—	—
Asthenia	1 (0.8)	1 (0.8)	—	—
Fever	1 (0.8)	—	—	—
Ulcer[b]	—	2 (12)	—	—
Heartburn/dyspepsia[b]	1 (6)	1 (6)	—	—
Allergy[b]	—	1 (6)	—	—

ALT: alanine aminotransferase; AST: aspartate aminotransferase.
[a] The number of treatment weeks with toxicity out of 133 total treatment weeks (%).
[b] The number of patients with toxicity among 17 evaluable patients (%).

TABLE 3
Response to Treatment

Response	No. of patients (%)
Evaluable patients	16 (100.0)
PR	2 (12.5)
SD	2 (12.5)
PD	12 (75)
ORR (95% CI)	12% (0–27%)

PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate; 95% CI: 95% confidence interval.

pilot study of celecoxib and PIVI 5-FU. Three patients had locally advanced PDAC and 14 patients had metastatic disease; all patients had been pretreated with either single-agent gemcitabine (15 patients) or gemcitabine-based combinations (2 patients), and all had confirmed PD at the time of inclusion. The median patient age was 60 years (range, 35–68 years); and the Eastern Cooperative Oncology Group performance status was 0 in 6 patients, 1 in 10 patients, and 2 in 1 patient (Table 1).

All patients completed at least 1 treatment week (median, 4 weeks; range, 1–33 weeks). All patients and a total of 133 treatment weeks were evaluable for toxicity. Hematologic toxicity was negligible, with Grade 2 anemia observed in 4 of 133 treatment weeks and no episodes of neutropenia or thrombocytopenia $>$ Grade 1 observed (Table 2). Asymptomatic transaminase elevation was the most common nonhematologic toxicity: Elevated aspartate aminotransferase levels were observed in 6 treatment weeks (Grade 1), 4 treatment weeks (Grade 2), 1 treatment week (Grade 3), and 1 treatment week (Grade 4), respectively, whereas elevated alanine aminotransferase levels were observed in 7 treatment weeks (Grade 1), 5 treatment weeks (Grade 2), and 2 treatment weeks (Grade 3), respectively, leading to a 1-week treatment delay or 25% 5-FU dose reductions in 7 of 133 treatment weeks administered. No other nonhematologic toxicities $>$ Grade 2 were observed (Table 2). However, celecoxib administration was discontinued in 3 patients after a median of 2 treatment weeks (range, 1–4 treatment weeks) for the following reasons: esophageogastroduodenoscopy-confirmed duodenal ulcer or erosive duodenitis (2 patients) and Grade 2 heartburn and/or dyspepsia (1 patient). One additional patient discontinued treatment (both celecoxib and 5-FU) for a generalized urticarioid allergic reaction to 5-FU. All patients promptly recovered from toxicity on treatment discontinuation and appropriate medical treatment, and no episodes of gastrointestinal bleeding were observed.

Early disease progression and death ($\leq$ 4 weeks) occurred in 2 patients; neither death was considered treatment-related, and both patients were classified with PD at the time of death for all subsequent analyses. One additional patient withdrew from the protocol for personal reasons after 4 treatment weeks and could not be evaluated for response. Thus, 16 patients were evaluable for response: Two of 16 patients (12.5%), both with metastatic disease, achieved a confirmed PR that lasted 23 weeks and 68 weeks, respec-

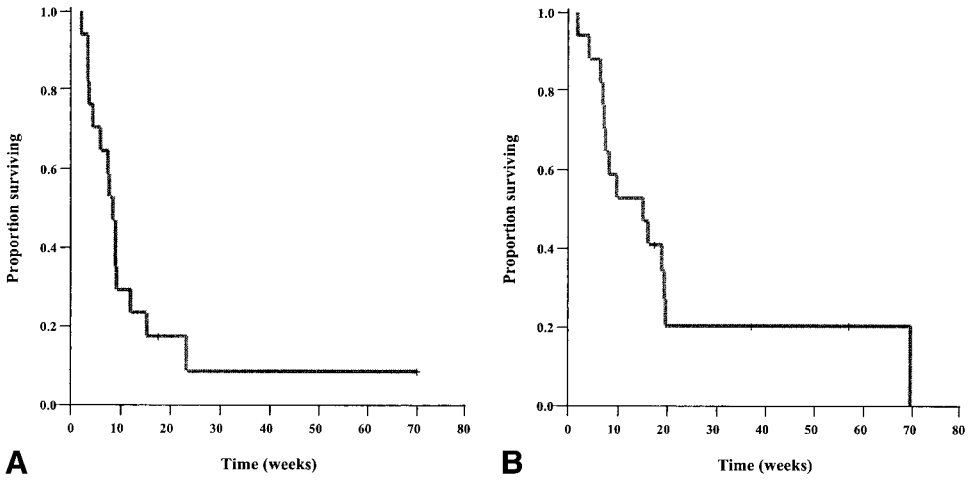

FIGURE 1. (A) Progression free survival and (B) overall survival curves for patients with pancreatic ductal adenocarcinoma who were treated with second-line celecoxib plus protracted intravenous infusion 5-fluorouracil (n = 17 patients).

tively; 2 of 16 patients (12.5%) had stable disease (SD) that lasted 10 weeks and 13 weeks, respectively; and 12 of 16 patients (75%) had PD. The overall response rate (ORR), according to an intent-to-treat analysis, was 12% (95% CI, 0–27%) (Table 3). In the 2 patients who experienced a PR to second-line celecoxib and PIVI 5-FU, the best responses to first-line single-agent gemcitabine were PD and SD of 19 weeks duration, respectively. Variations in serum CA 19.9 levels during treatment were evaluable in 9 patients, who had elevated levels at baseline and were monitored serially every 4 weeks: a significant decreases in CA 19.9 levels were observed in 3 patients (decreases $>$ 75% compared with baseline in 2 patients and a 50% decrease compared with baseline in 1 patient), whose objective responses to treatment were a PR, PD, and SD, respectively (data not shown). The median time to disease progression for the entire group of 17 patients was 8 weeks (range, 2–68 weeks), and the median OS was 15 weeks (range, 2–70 weeks) (Fig. 1).

DISCUSSION

Despite the introduction of gemcitabine and attempts at developing combination chemotherapy regimens, pancreatic carcinoma remains a chemoresistant tumor. Although it is used widely in patients with metastatic PDAC, bolus administration of 5-FU is reported to have little activity in this disease.[31] Because 5-FU is a cell cycle-specific agent with a short duration of action, investigators have attempted to improve the efficacy of this drug using infusional or chronomodulated administration or with the addition of folinic acid. Unfortunately, to our knowledge, there has been no clear evidence of additional clinical benefit with these strategies, with response rates ranging between 0% and 13% and median survival ranging between 10 weeks and 26 weeks in chemotherapy-naïve patients.[31–35] Therefore, manipulations that have improved the activity of 5-FU in other malignancies remain of uncertain benefit in patients with PDAC.

Herein, we provide what to our knowledge is the first report concerning the combination of celecoxib and PIVI 5-FU in patients with advanced, gemcitabine-resistant/refractory PDAC. Treatment-related toxicity was minimal and manageable, making this combination very attractive in an essentially palliative setting, such as advanced PDAC. In particular, the absence of hand-foot syndrome and the very low incidence of diarrhea and hematologic toxicities are in keeping with reports in patients with colorectal carcinoma, suggesting that the addition of celecoxib to 5-FU-based or capecitabine-based regimens actually may result in a lower-than-expected toxicity rate.[36–38] However, 3 patients developed upper gastrointestinal toxicity, requiring celecoxib discontinuation; this finding is relatively surprising in that it was not observed in a recently reported study of preoperative celecoxib combined with paclitaxel/carboplatin in patients with nonsmall cell lung carcinoma[39] and occurred early in the course of treatment (after 1–4 treatment weeks). In patients with advanced PDAC, biliary reflux, abnormal gastric motility with delayed emptying, and gastric outlet obstruction all may represent relevant predisposing factors that cause chronic injury to the gastric mucosa, thereby rendering it more susceptible to COX inhibition-mediated damage.

Encouraging preliminary activity also was observed in this pilot study, with 2 durable, clinically meaningful, objective responses and a median survival of 15 weeks reported in the entire population. These results are comparable with those obtained with gemcitabine as second-line treatment in patients with 5-FU-refractory PDAC (ORR, 10.5%; median OS, 16.5 weeks),[40] and they suggest that the combination of COX-2 inhibitors and

infusional 5-FU has detectable, although minimal, activity in advanced PDAC. Assessing the relative contribution of celecoxib and infusional 5-FU to the overall activity of the regimen was beyond the scope of the current study and will require properly designed, randomized trials; however, it is interesting to note that no objective responses were observed in a previous study of a similar regimen of PIVI 5-FU alone in patients with chemotherapy-naïve PDAC,[32] suggesting that COX-2 inhibition indeed may have contributed to the activity observed in an even more advanced, gemcitabine-resistant/refractory patient population. This hypothesis is supported by preclinical evidence that celecoxib potentiates 5-FU antitumor effects in animal models[16] and by preliminary clinical evidence from a retrospective analysis of a cohort of patients with metastatic colorectal carcinoma who were treated with capecitabine with or without celecoxib: In that study, the results suggested that celecoxib may improve capecitabine antitumor efficacy.[38]

The results of this exploratory study indicate that the combination of celecoxib and PIVI 5-FU is feasible and demonstrates encouraging preliminary activity even in a population of chemotherapy-pretreated patients with far advanced PDAC. These findings add to the growing body of evidence suggesting that COX-2 may be developed into a clinically relevant, therapeutic target in these and other diseases,[41] and further exploration is warranted of COX-2 inhibitor/fluoropyrimidine combinations in patients with inoperable PDAC.

REFERENCES

1. Chan G, Boyle JO, Yang EK, et al. Cyclooxygenase-2 expression is up-regulated in squamous cell carcinoma of the head and neck. *Cancer Res.* 1999;59:991–994.
2. Soslow RA, Dannenberg AJ, Rush D, et al. COX-2 is expressed in human pulmonary, colonic, and mammary tumors. *Cancer.* 2000;89:2637–2645.
3. Wolff H, Saukkonen K, Anttila S, Karjalainen A, Vainio H, Ristimaki A. Expression of cyclooxygenase-2 in human lung carcinoma. *Cancer Res.* 1998;58:4997–5001.
4. Koki AT, Masferrer JL. Celecoxib: a specific COX-2 inhibitor with anticancer properties. *Cancer Control.* 2002;9:28–35.
5. Cao Y, Prescott SM. Many actions of cyclooxygenase-2 in cellular dynamics and in cancer. *J Cell Physiol.* 2002;190: 279–286.
6. Pai R, Soreghan B, Szabo IL, Pavelka M, Baatar D, Tarnawski AS. Prostaglandin E2 transactivates EGF receptor: a novel mechanism for promoting colon cancer growth and gastrointestinal hypertrophy. *Nat Med.* 2002;8:289–293.
7. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. *Epidemiology.* 1994;5:138–146.
8. Anderson KE, Johnson TW, Lazovich D, Folsom AR. Association between nonsteroidal anti-inflammatory drug use and the incidence of pancreatic cancer. *J Natl Cancer Inst.* 2002; 94:1168–1171.
9. Langman MJ, Cheng KK, Gilman EA, Lancashire RJ. Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. *BMJ.* 2000;320:1642–1646.
10. Schernhammer ES, Kang JH, Chan AT, et al. A prospective study of aspirin use and the risk of pancreatic cancer in women. *J Natl Cancer Inst.* 2004;96:22–28.
11. Niijima M, Yamaguchi T, Ishihara T, et al. Immunohistochemical analysis and in situ hybridization of cyclooxygenase-2 expression in intraductal papillary-mucinous tumors of the pancreas. *Cancer.* 2002;94:1565–1573.
12. Okami J, Yamamoto H, Fujiwara Y, et al. Overexpression of cyclooxygenase-2 in carcinoma of the pancreas. *Clin Cancer Res.* 1999;5:2018–2024.
13. Tucker ON, Dannenberg AJ, Yang EK, et al. Cyclooxygenase-2 expression is up-regulated in human pancreatic cancer. *Cancer Res.* 1999;59:987–990.
14. Molina MA, Sitja-Arnau M, Lemoine MG, Frazier ML, Sinicrope FA. Increased cyclooxygenase-2 expression in human pancreatic carcinomas and cell lines: growth inhibition by nonsteroidal anti-inflammatory drugs. *Cancer Res.* 1999;59: 4356–4362.
15. Yip-Schneider MT, Barnard DS, Billings SD, et al. Cyclooxygenase-2 expression in human pancreatic adenocarcinomas. *Carcinogenesis.* 2000;21:139–146.
16. Moore RJ, Zweifel BS, Huevelman DM, et al. Enhanced antitumor activity by co-administration of celecoxib and the chemotherapeutic agents cyclophosphamide and 5-FU. *Proc Am Assoc Cancer Res.* 2000;41:409.
17. Yip-Schneider MT, Sweeney CJ, Jung SH, Crowell PL, Marshall MS. Cell cycle effects of nonsteroidal anti-inflammatory drugs and enhanced growth inhibition in combination with gemcitabine in pancreatic carcinoma cells. *J Pharmacol Exp Ther.* 2001;298:976–985.
18. Haycox A, Lombard M, Neoptolemos J, Walley T. Review article: current treatment and optimal patient management in pancreatic cancer. *Aliment Pharmacol Ther.* 1998;12:949–964.
19. el Kamar FG, Grossbard ML, Kozuch PS. Metastatic pancreatic cancer: emerging strategies in chemotherapy and palliative care. *Oncologist.* 2003;8:18–34.
20. Palmer KR, Kerr M, Knowles G, Cull A, Carter DC, Leonard RC. Chemotherapy prolongs survival in inoperable pancreatic carcinoma. *Br J Surg.* 1994;81:882–885.
21. Glimelius B, Hoffman K, Sjoden PO, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol.* 1996;7:593–600.
22. Mallinson CN, Rake MO, Cocking JB, et al. Chemotherapy in pancreatic cancer: results of a controlled, prospective, randomised, multicentre trial. *BMJ.* 1980;281:1589–1591.
23. Cullinan S, Moertel CG, Wieand HS, et al. A Phase III trial on the therapy of advanced pancreatic carcinoma. Evaluations of the Mallinson regimen and combined 5-fluorouracil, doxorubicin, and cisplatin. *Cancer.* 1990;65:2207–2212.
24. [No authors listed.] Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. Meta-Analysis Group in Cancer. *J Clin Oncol.* 1998;16:3537–3541.
25. [No authors listed.] Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. Meta-Analysis Group in Cancer. *J Clin Oncol.* 1998;16:301–308.
26. Hidalgo M, Castellano D, Paz-Ares L, et al. Phase I–II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer. *J Clin Oncol.* 1999;17:585–592.

27. Auerbach M, Wampler GL, Lokich JJ, Fryer D, Fryer JG, Ahlgren JD. Treatment of advanced pancreatic carcinoma with a combination of protracted infusional 5-fluorouracil and weekly carboplatin: a Mid-Atlantic Oncology Program study. *Ann Oncol.* 1997;8:439–444.
28. Maisey N, Chau I, Cunningham D, et al. Multicenter randomized Phase III trial comparing protracted venous infusion (PVI) fluorouracil (5-FU) with PVI 5-FU plus mitomycin in inoperable pancreatic cancer. *J Clin Oncol.* 2002;20:3130–3136.
29. Reni M, Passoni P, Panucci MG, et al. Definitive results of a Phase II trial of cisplatin, epirubicin, continuous-infusion fluorouracil, and gemcitabine in Stage IV pancreatic adenocarcinoma. *J Clin Oncol.* 2001;19:2679–2686.
30. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer.* 1981;47:207–214.
31. Burris HA III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol.* 1997;15:2403–2413.
32. Tajiri H, Yoshimori M, Okazaki N, Miyaji M. Phase II study of continuous venous infusion of 5-fluorouracil in advanced pancreatic cancer. *Oncology.* 1991;48:18–21.
33. DeCaprio JA, Mayer RJ, Gonin R, Arbuck SG. Fluorouracil and high-dose leucovorin in previously untreated patients with advanced adenocarcinoma of the pancreas: results of a Phase II trial. *J Clin Oncol.* 1991;9:2128–2133.
34. Crown J, Casper ES, Botet J, Murray P, Kelsen DP. Lack of efficacy of high-dose leucovorin and fluorouracil in patients with advanced pancreatic adenocarcinoma. *J Clin Oncol.* 1991;9:1682–1686.
35. Weinerman BH, MacCormick RE. A Phase II survival comparison of patients with adenocarcinoma of the pancreas treated with 5-fluorouracil and calcium leucovorin versus a matched tumor registry control population. *Am J Clin Oncol.* 1994;17:467–469.
36. Blanke CD, Benson AB III, Dragovich T, et al. A Phase II trial of celecoxib (CX), irinotecan (I), 5-fluorouracil (5FU), and leucovorin (LCV) in patients (pts) with unresectable or metastatic colorectal cancer (CRC). *Proc Am Soc Clin Oncol.* 2002;21:127a.
37. Sweeney C, Seitz D, Ansari R, et al. A Phase II trial of irinotecan (I), 5-fluorouracil (F), leucovorin (L) (IFL), celecoxib and glutamine as first line therapy for advanced colorectal cancer: a Hoosier Oncology Group Study. *Proc Am Soc Clin Oncol.* 2002;21:105b.
38. Lin E, Morris JS, Ayers GD. Effect of celecoxib on capecitabine-induced hand-foot syndrome and antitumor activity. *Oncology (Huntingt).* 2002;16:31–37.
39. Altorki NK, Keresztes RS, Port JL, et al. 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.* 2003;21:2645–2650.
40. Rothenberg ML, Moore MJ, Cripps MC, et al. A Phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. *Ann Oncol.* 1996;7:347–353.
41. Dmitrovsky E. Combining cytotoxic chemotherapy with cyclooxygenase-2 inhibition. *J Clin Oncol.* 2003;21:2631–2632.