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ORIGINAL ARTICLE

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A phase I trial of celecoxib in combination with docetaxel and irinotecan in patients with advanced cancer

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Abstract *Purpose*: This phase I study was conducted to determine the safety, tolerability and maximum tolerated dose of the combination of celecoxib, a selective cyclooxygenase-2 inhibitor, with docetaxel and irinotecan, in patients with advanced solid tumors. *Patients and methods*: Patients with solid tumors received one of three escalating dose levels of daily celecoxib in combination with docetaxel and irinotecan administered on days 1 and 8 of an every 21-day cycle. Toxicities were graded by the National Cancer Institute Common Toxicity Criteria (NCI CTC) and recorded as maximum grade per patient for each treatment cycle. *Results*: A total of 19 patients received 90 cycles of treatment through three dose levels. Dose-limiting toxicities were nausea and diarrhea. The most common treatment-related toxicities in all cycles of treatment were alopecia, fatigue, diarrhea, nausea, vomiting, anemia, anorexia, and edema.. The maximum tolerated dose was established at celecoxib 400 mg twice a day continuously, weekly docetaxel 30 mg/m^2 and irinotecan 50 mg/m^2 for 2 weeks every 21 days. Disease stabilization (five or more cycles) was documented in eight patients. *Conclusion*: The combination of celecoxib with docetaxel and irinotecan did not ameliorate irinotecan-induced diarrhea. Although prolonged disease stabilization was achieved in some patients, we do not recommend combining celecoxib with docetaxel and irinotecan because of lack of activity and the side effect profile of this combination.

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Introduction

The cyclooxygenase (COX) enzyme, also known as prostaglandin-endoperoxide synthase (PTGS), is a key enzyme involved in the synthesis of prostaglandins from arachidonic acid. There are two isoforms of COX [1]. COX-1 is constitutively expressed in most tissues and appears to mediate various physiologic functions [1, 2]. By contrast, COX-2 is undetectable in most normal tissues but is rapidly induced by oncogenes, growth factors, cytokines, and tumor promoters [3–9].

COX-2 is commonly overexpressed in premalignant and malignant tissues, and thus is implicated in the pathogenesis and evolution of a variety of cancers [7, 10–12]. COX-2-derived prostanoids have been shown to modulate cytokine synthesis, to influence cell proliferation and apoptosis, to modulate the nuclear translocation and function of tumor suppressor gene products, and to influence angiogenesis [12–19].

Docetaxel belongs to the taxane class of antimicrotubule chemotherapeutic drugs that bind to tubulin and retard microtubule depolymerization, impair mitosis, block cell cycle progression, and facilitate apoptosis. Among the multiple other cellular effects seen with taxane therapy is the induction of genes, among which is the COX-2 gene [20, 21]. This is relevant as stimulating the formation of cytoprotective prostaglandins by COX-2 could blunt apoptosis [17] and contribute to chemoresistance.

On the other hand, irinotecan is a topoisomerase I inhibitor that has been shown to be highly effective in the treatment of various malignancies such as colon, gastric, lung and pancreatic cancers. Mouse tumor models demonstrate that celecoxib enhances the antitumor effect of CPT-11 and effects a dose-dependent reduction in the severity of late diarrhea in a rat model [22].

Preclinical studies have demonstrated a greater than additive cytotoxic effect of the combination of docetaxel and irinotecan [23, 24]. Subsequent clinical studies produced encouraging results in various tumor types [25–30]. In a phase I study performed by our group evaluating the combination of docetaxel and irinotecan [26], the recommended phase II dose was irinotecan 160 mg/m^2 and docetaxel 65 mg/m^2, administered every 3 weeks. However, in spite of promising antitumor activity, significant toxicities were seen. Severe grade 3 or 4 neutropenia was seen in 12 of 18 patients (42 events out of 85 courses). Dose-dependent diarrhea was encountered in 14 of 18 patients (44 events out of 85 courses) [26]. It was hypothesized that using a weekly schedule of this combination may be better tolerated [29, 30]. In addition, preclinical studies had suggested that addition of celecoxib may not only potentially reduce severity and frequency of diarrhea but also enhance the antitumor activity of the combination of docetaxel and irinotecan. We therefore undertook this phase I study to evaluate the safety, tolerability and potential clinical activity of docetaxel and irinotecan given on days 1 and 8 on an every 21-day scheduled in combination with daily oral celecoxib.

Patients and methods

Patient selection

Patients with histologic or cytologic evidence of metastatic or locally advanced cancer for which no effective treatment exists, or who were unresponsive to currently available therapy, and had measurable or evaluable disease were eligible for this study. Other inclusion criteria were age ≥18 years; expected survival of at least 3 months; Eastern Cooperative Oncology Group performance status ≤2; adequate bone marrow function (platelets ≥100×10^9/l, absolute neutrophil count ≥1.5×10^9/l, hemoglobin ≥8.0 g/dl), hepatic function (total bilirubin ≤1.5 times the upper limit of normal, ALT ≤2.5 times the upper limit of normal) and renal function (stable serum creatinine ≤1.5 times the upper limit of normal); no chemotherapy, radiotherapy, biologic, hormonal or investigational drug therapy within 28 days prior to study entry; >6 weeks must have elapsed since prior nitrosourea or mitomycin C chemotherapy. Patients who had significant pulmonary or cardiovascular disease, poorly controlled diabetes mellitus, prior treatment with regimens requiring radiation therapy to >25% of the bone marrow, prior chemotherapy with both irinotecan and docetaxel, history of grade 3 or worse hypersensitivity to docetaxel or its vehicle (Tween 80), active brain metastasis, or an active infection requiring therapy were excluded from this trial. Written informed consent was obtained according to federal and institutional guidelines.

Treatment and clinical care of patients

Each patient received sequential intravenous infusions of docetaxel and irinotecan according to the assigned dose level (Table 1). Docetaxel was supplied by Aventis Pharmaceuticals in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution. It was initially diluted to a concentration of 10 mg/ml using the accompanying sterile, non-pyrogenic diluent (13% ethanol in water for injection) as instructed by the manufacturer. Final dilution with 250 ml 0.9% sodium chloride solution or 5% dextrose solution to a concentration not exceeding 0.74 mg/ml docetaxel was prepared prior to drug administration. Irinotecan was supplied by Pharmacia (later acquired by Pfizer) in single-dose 2-ml or 5-ml vials containing 40 mg or 100 mg of irinotecan, respectively. The calculated dose for each patient was then diluted in 500 ml of D5W. Celecoxib was supplied as capsules of 100 mg or 200 mg by Pharmacia (Pfizer) and taken without regard to meals. Irinotecan was administered first over 90 min followed immediately by docetaxel over 60 min. Premedication with oral dexamethasone is standard to decrease incidence of fluid retention seen with docetaxel.

Celecoxib was administered as a fixed twice-daily oral dose continuously (days 1–21). Irinotecan and docetaxel were administered on days 1 and 8 of each 21-day cycle. At least three new patients were entered at each dose level in a standard "cohorts-of-three" phase I design [31]. A total of 12 patients were accrued at the maximum tolerated dose (MTD) to better define the toxicity of this regimen, and potentially perform correlative studies, if the regimen was found to be promising. Dose escalation was not allowed in individual patients.

Complete patient histories, physical examinations, complete blood cell counts, serum electrolytes, chemistries, urinalysis and electrocardiograms were performed at baseline and prior to each course of treatment. Complete blood counts were repeated weekly while patients were on study. Radiologic studies (roentgenograms, computed axial tomographic scans, magnetic resonance imaging) were performed at baseline and after every two cycles of therapy to assess tumor response.

Table 1 Dose escalation

Dose level	Number	Celebrex (mg twice daily)	CPT-11 (mg/m^2)	Docetaxel (mg/m^2)	Cycles	Dose limiting toxicities
1[a]	3	400	50	25	9	0
2[b]	13	400	50	30	69	2
3	3	400	50	35	12	2

[a]One patient was replaced on dose level 1
[b]Maximum tolerated dose, MTD

A maximum of three measurable lesions were identified as target lesions at baseline. A complete or partial response required the disappearance of all evidence of tumor or at least a 30% reduction in the sum of the longest diameter of all target lesions from the baseline measurement, respectively, confirmed by repeat studies performed at least 6 weeks after the criteria for response were first met. Progressive disease was the appearance of new lesion(s) or an increase in the sum of the longest diameter of all target lesions by at least 20% from baseline. Stable disease was documented when there was persistence of disease without meeting the criteria for progression, partial response or complete response.

Dose-limiting toxicity

All toxicities were graded according to the National Cancer Institute common toxicity criteria (NCI CTC version 2.0). The MTD was defined as one dose level below the dose that induced dose-limiting toxicities (DLT) in more than one-third of patients (at least two of a maximum of six patients). Severe or life-threatening NCI CTC grades 3 or 4 non-hematologic toxicity (with the exception of fatigue, myalgias/arthralgias, alopecia, nausea and vomiting, grade 3 injection site reactions, hypersensitivity reactions) were considered dose-limiting. NCI CTC grade 3 or 4 nausea and vomiting in patients who had received prophylactic treatment with an optimal antiemetic regimen was considered dose-limiting. An absolute neutrophil count $<0.5\times10^9$/l associated with fever or lasting for more than five consecutive days, platelet count of $<0.25\times10^9$/l of any duration or between 25×10^9/l and 50×10^9/l associated with hemorrhage requiring blood transfusion, and treatment delay of more than 1 week because of failure to adequately recover from the previous cycle were also considered dose-limiting.

Results

Patient demographics

A total of 19 patients (Table 2) received 90 cycles of therapy through three dose levels. This excludes one patient who received partial treatment at dose level 1. He did not complete the first cycle as he succumbed to a non-treatment related death from superior mesenteric artery thrombosis secondary to his underlying atrial fibrillation. Twelve females and seven males with a median age of 58 years (range 35–74 years) were accrued to determine and evaluate the MTD for this combination. The median number of cycles administered per patient was four (range 1–14). Eight patients completed five or more cycles of therapy. Of the 19 patients, 17 (89%) had a good performance status (0 or 1), 17 had received prior chemotherapy and 8 had received prior radiation therapy. The most common tumor types were lung, pancreas, head and neck squamous cell carcinoma, and ovarian cancer.

Table 2 Patient demographics

Variable	Value
Gender, *N* (%)	
F	12 (63%)
M	7 (37%)
Age (years)	
Median	58
Range	35–74
ECOG performance status, *N* (%)	
0	9 (47%)
1	8 (42%)
2	2 (11%)
Cycles of treatment, *N* (%)	
1	1 (5%)
2	8 (42%)
4	2 (11%)
6	2 (11%)
7	1 (5%)
8	4 (21%)
14	1 (5%)
Cycles of treatment, *N*	
Median	4
Range	1–14
Prior therapies, *N* (%)	
Chemotherapy	17 (89%)
Surgery	11 (58%)
Radiation therapy	8 (42%)
Hormone therapy	3 (16%)
Immunotherapy	1 (5%)
Tumor type, *N* (%)	
Head and neck squamous cell	3 (16%)
Ovarian	3 (16%)
Lung	3 (16%)
Pancreatic	3 (16%)
Colorectal	2 (11%)
Others	5 (26%)

Toxicities

Hematologic toxicity The hematologic effects of celecoxib in combination with docetaxel and irinotecan and the number of patients experiencing various grades of toxicity are shown in Fig. 1. Anemia, mostly grade 1, was the most common hematologic toxicity. Out of 90 treatment cycles, neutropenia was encountered only twice, both events being severe (grade 3). No patient had thrombocytopenia.

Gastrointestinal toxicity Diarrhea, of varying severity but mostly grade 1, was seen in all except one patient (Fig. 2). Of the 19 patients, 5 (26%) had grade 3 or worse diarrhea. Grade 3 diarrhea in spite of antidiarrheals was encountered among all four patients who had DLT in the first cycle of dose levels 2 and 3. Nausea, mostly grade 1, was experienced in over half of the treatment courses (50/90). One of the four aforementioned patients had dose-limiting nausea in addition to grade 3 diarrhea. Vomiting, mostly grade 1 as well, was less frequently encountered (20/90). Abdominal pain was rarely encountered.

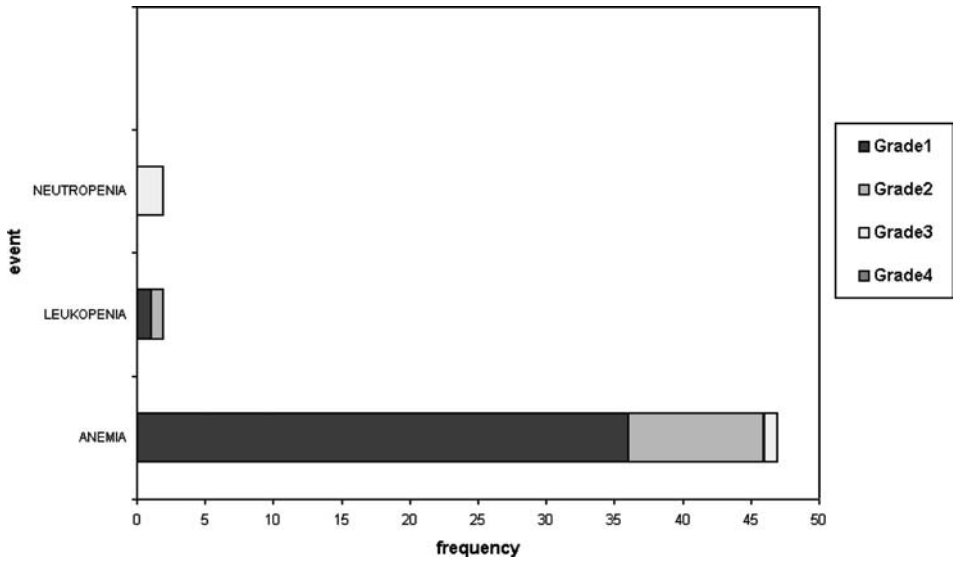

Fig. 1 Treatment-related hematologic toxicities in all cycles

Other toxicities Severe fatigue warranting dose reduction was seen in a patient with esophageal cancer who had the longest duration of disease stabilization. Fatigue was noted in over half of the treatment courses (56/90), most of which were grade 1 (32/90) and 2 (22/90). Mild sensory neuropathy was observed in approximately one-fifth of the patients. Alopecia was common.

Antitumor activity

No partial or complete responses were seen. Ten patients received four or more cycles of therapy, out of which five (pancreatic, tonsillar, adrenal, NSCLC, esophageal cancer) received more than eight cycles of therapy. Eight of the patients had stable disease for more than four cycles. A patient with metastatic esophageal cancer previously treated with gemcitabine, cisplatin and a farnesyltransferase inhibitor had a sustained disease stabilization of approximately 10.5 months.

Discussion

The MTD on this schedule is celecoxib 400 mg twice daily given with docetaxel 30 mg/m^2 and irinotecan 50 mg/m^2 on days 1 and 8 of each 21-day cycle. This is comparable to the regimen reported by Yamamoto et al. [27]. In their study, docetaxel 60 mg/m^2 (day 8) and irinotecan 60 mg/m^2 (days 1 and 8) repeated every 21 days were administered to patients with NSCLC [27], which was a modification of the original schedule reported

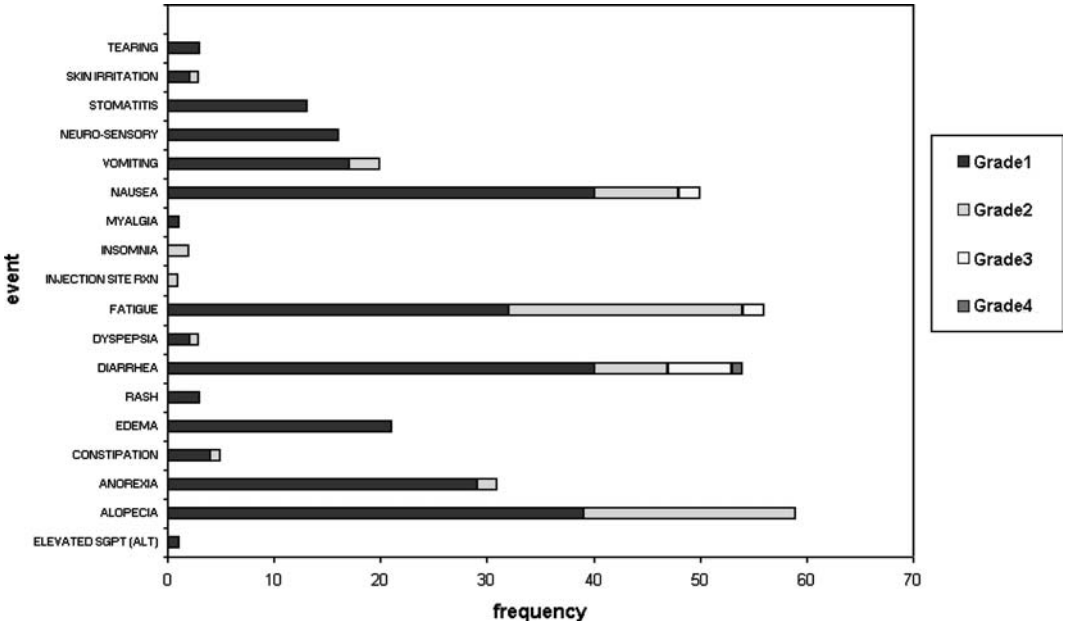

Fig. 2 Treatment-related non-hematologic toxicities in all cycles

previously by the same group in the hope of reducing hematologic toxicity [28]. Despite the omission of day-15 irinotecan and the change from day 2–8 of docetaxel, the severe neutropenia and febrile neutropenic events that were encountered remained significant. This is in contrast to our study where neutropenia was rare in this heavily pretreated population. The reduced incidence of neutropenia may have been a consequence of the increased tolerability of weekly docetaxel administration as opposed to the schedule used by the Japanese investigators. This is consistent with the results reported by Lordick et al. [29] in patients with esophageal cancer refractory to treatment. Myelosuppression seen with the original schedule of once every 3 weeks prompted the investigators to alter drug administration to a weekly schedule, and this resulted in a dramatic reduction in hematologic toxicity. Similar low rates of grade 3/4 hematologic toxicity ($< 10\%$) were reported by Font et al. [30] in NSCLC patients receiving the weekly combination as second-line therapy.

Abdominal pain is rarely seen in spite of the higher doses of celecoxib used. However, diarrhea remains a common, if not universal, adverse effect seen with this combination. Despite the plausible benefit of celecoxib in reducing diarrhea associated with irinotecan, grade 3/4 diarrhea occurred in 26% of our patients, compared to 12.5%, 16% and 25% reported by Lordick et al. [29], Yamamoto et al. [27] and Font et al. [30], respectively, using similar variations of weekly irinotecan with docetaxel administration. Diarrhea is a side effect that may arise from celecoxib use itself [32]. Thus, this study does not support the touted effect of celecoxib in abating the gastrointestinal toxicity seen with irinotecan.

Celecoxib did not seem to contribute significant cytotoxic activity to the combination of docetaxel and irinotecan. Indeed, although phase I trials are not designed to evaluate antitumor efficacy, the lack of objective responses with two active chemotherapy agents in this study was disappointing. Moreover, toxicity was relatively significant. Taken together, the combination of docetaxel, irinotecan and celecoxib cannot be recommended for further study.

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