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ORIGINAL ARTICLE

Phase I dose-escalating study of biweekly fixed-dose rate gemcitabine plus pemetrexed in patients with advanced solid tumors

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Abstract
Purpose To determine the maximum tolerated dose (MTD) and the recommended phase II dose and to identify the dose-limiting toxicities (DLTs) of gemcitabine, administered by fixed-dose rate (FDR) infusion, combined with the antifolate agent pemetrexed in patients with advanced solid tumors.
Methods Eligible patients were entered into this open label, phase I trial. Using a 3 + 3 dose escalation design, patients received intravenous pemetrexed 300–800 mg/m^2 followed by FDR gemcitabine 900–1,500 mg/m^2 at 10 mg/m^2/min on Day 1 every 2 weeks. All patients received folic acid and vitamin B_{12} supplementation. Patients continued until DLT or disease progression.
Results A total of 33 patients were treated at 7 dose levels with a total of 230 cycles (median: 4 cycles; mean: 7 cycles; range: 1–35 cycles). The MTD of the combination was pemetrexed 800 mg/m^2 and gemcitabine 1,500 mg/m^2 over 150 min. DLTs were febrile neutropenia and grade 3 renal failure. Of the 28 patients evaluable for response, 3 patients experienced a partial response (10.7%) and 13 patients had stable disease (46.4%); the disease control rate was 57.1%.
Conclusions The recommended phase II dose for biweekly pemetrexed with FDR gemcitabine is 800 mg/m^2 and 1,200 mg/m^2 × 120 min, respectively. This regimen allows good dose intensity of both drugs to be administered on a simple schedule with an excellent tolerability profile. This regimen showed moderate activity in a diverse phase I population, possibly greater than either single agent. Further assessment of the combination in a phase II setting is suggested.

Keywords Pemetrexed · Fixed-dose rate · Gemcitabine · Advanced solid tumors · Dose-limiting toxicity · Maximum tolerated dose

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Introduction

Gemcitabine is a pyrimidine antimetabolite with broad-spectrum antineoplastic activity against solid tumors and hematologic malignancies [1]. In clinical studies, gemcitabine alone or in combination with other chemotherapeutic agents has shown activity across a variety of tumor types including lung, head and neck, breast, ovary, pancreas, bladder, and sarcoma. Gemcitabine has been the standard chemotherapy agent for patients with advanced pancreatic cancer since receiving US Food and Drug Administration (FDA) approval in 1997. Since then, the FDA has also approved its use for the treatment of advanced breast, lung, and ovarian cancers.

Fixed dose rate (FDR) administration of gemcitabine is of interest due to its potential to improve objective tumor response rates by increasing intracellular levels of active, phosphorylated gemcitabine metabolites. Given the saturable and rate-limiting kinetics of gemcitabine phosphorylation, FDR infusion (10 mg/m^2/min) results in higher intracellular concentrations and theoretically offers better activity than the commonly used 30-min infusion [2].

Tempero et al. [3] performed a direct comparison of 2 gemcitabine delivery schemes in patients with chemotherapy-naïve pancreatic cancer. Gemcitabine was administered either at a dose of 2,200 mg/m^2 with standard infusion over 30 min or at FDR 1,500 mg/m^2 for 150 min at a constant dosing rate of 10 mg/m^2/min. Both arms were delivered weekly for 3 weeks every 4 weeks. While grade 3–4 hematologic toxicity was significantly greater for FDR gemcitabine compared to standard gemcitabine infusion, results suggested a trend toward improved response rate and survival for FDR gemcitabine. In addition, the pharmacokinetics provided proof of concept that FDR infusion results in greater formation of the active gemcitabine metabolites as measured in peripheral blood mononuclear cells of the 6 patients studied. This approach has been used in other tumor types as well [8].

FDR administration of gemcitabine has been studied in a variety of tumor types and combined with many different chemotherapeutic agents. For example, biweekly FDR gemcitabine 1,200 mg/m^2 plus oxaliplatin 85 mg/m^2 is active and well tolerated in advanced non-small-cell lung cancer (NSCLC), resulting in 23% of patients with a partial response (PR), median overall survival of 10.4 months, and a 1-year survival rate of 42% [4]. The combination of biweekly FDR gemcitabine 1,000 mg/m^2 plus oxaliplatin 100 mg/m^2 (GEM-OX) has been widely studied in phase III trials for pancreatic cancer both by the Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) in France [5] and the Eastern Cooperative Oncology Group (ECOG) [6]. In the latter study, gemcitabine given by FDR showed a longer progression-free survival (PFS) and time to treatment failure (TTF) compared with standard gemcitabine infusion over 30 min, and was equivalent to the GEM-OX, although not statistically significant due to the 2-way comparisons requiring $P < 0.025$. FDR gemcitabine with cisplatin 20 mg/m^2 on Days 1 and 8 of a 21-day cycle is well tolerated in metastatic pancreatic cancer, resulting in 19% PR, 59.6% stable disease (SD), median survival of 7.1 months, and an estimated 1-year survival rate of 29% in one phase II trial [7]. We and others previously reported phase I studies using FDR gemcitabine 10 mg/m^2/min in combination with irinotecan with activity seen in both cases [9, 10, 11].

Pemetrexed is a multitargeted antifolate that inhibits folate-dependent enzymes, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase [12]. A 10-min infusion once every 21 days was the schedule that allowed the delivery of the highest dose intensity [13]. Dose-limiting toxicities (DLTs) were neutropenia, thrombocytopenia, and fatigue, although these improved substantially with the addition of vitamin B_{12} and folic acid supplementation. Pemetrexed demonstrates linear pharmacokinetics over a wide dose range from 50 to 700 mg/m^2 [13]. The FDA-approved dose is pemetrexed 500 mg/m^2 given as a 10-min infusion once every 21 days and is approved for the treatment of inoperable malignant mesothelioma and metastatic NSCLC, in both the first- and second-line setting. In addition, pemetrexed has demonstrated activity against a broad spectrum of solid tumors, including breast, pancreatic, renal, gastric, colorectal, head and neck, bladder, and cervical cancer.

The combination of pemetrexed and gemcitabine has been evaluated in various solid tumors, including mesothelioma and pancreatic cancer, demonstrating clinical activity in phase II and phase III studies. The 3-week schedule of gemcitabine on Days 1 and 8 with pemetrexed on Day 8 has most commonly been adopted for these trials [14, 15]. In pancreatic cancer, a phase III trial did not show a benefit for the addition of pemetrexed using this schedule. A biweekly schedule has also been reported in NSCLC [16, 17], bladder [18] and ovarian cancers [19], with a favorable toxicity profile and promising activity.

The primary objectives of this phase I dose-escalating study were to determine the maximum tolerated dose (MTD), the recommended phase II dose (for future phase II studies), and the DLTs of intravenously administered pemetrexed followed by FDR gemcitabine infusion, every 14 days, in the treatment of patients with advanced solid tumors. Documentation of antitumor activity for this drug combination was a secondary objective.

Patients and methods

Selection of patients

Enrolled patients were ≥18 years of age with histologically or cytologically confirmed advanced or metastatic solid tumors refractory to standard treatments, had received not more than 2 prior chemotherapy regimens, and had an estimated life expectancy of ≥12 weeks. All patients were eligible regardless of measurability of disease, but response was assessed only in those with measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) [20]. Patients were required to have an ECOG performance status of 0 or 1, adequate hematologic (defined as absolute neutrophil count [ANC] ≥1,500/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9 g/dL), hepatic (bilirubin <1.5 times the upper limit of normal [×ULN],

aspartate transaminase (AST) and alanine transaminase (ALT) <3.0 × ULN if liver metastases were not present or <5 × ULN if liver metastases were present), and renal (creatinine clearance [CrCl] ≥45 mL/min) functions. Prior surgery or radiotherapy to <25% of bone marrow was allowed. Patients could not have received radiotherapy ≤1–2 weeks before entering the study, and must have recovered from the acute toxic effects of any previous chemotherapy or radiotherapy prior to enrollment.

Patients were excluded if they met any of the following criteria: received treatment ≤30 days before study entry with any investigational drug; previously treated with pemetrexed or gemcitabine; pregnant or breast-feeding; serious concomitant systemic disorders that, in the opinion of the investigator, would compromise the safety of the patient or compromise the patient's ability to complete the study; inability to interrupt aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) for more than 5 days; symptomatic brain metastases; presence of clinically relevant third-space fluid collection that could not be controlled by drainage or other procedures prior to study entry; and inability or unwillingness to take folic acid, vitamin B_{12} supplementation, or dexamethasone.

Written informed consent was obtained from all patients prior to undergoing any study procedure or receiving any study treatment. This study was approved by the institutional review board of the New York University Medical Center prior to enrolling patients and was conducted in accordance with the ethical principles of the Declaration of Helsinki, with the principles of good clinical practice, and with all applicable laws and regulations.

Study design

The study was an open-label, single-center, non-randomized, dose-escalating phase I trial to evaluate the safety of combined pemetrexed and FDR infusion gemcitabine for the treatment of advanced solid tumors. The primary endpoints were the determination of DLT frequencies, the MTD, and the recommended phase II dose for the combination. The secondary endpoint was assessment of response rate for those patients with measurable disease.

Treatment plan

Pemetrexed was administered by intravenous infusion over 10 min on Day 1 of each 14-day cycle with a starting dose of pemetrexed 300 mg/m^2. Gemcitabine was administered intravenously on the same day following pemetrexed at a FDR of 10 mg/m^2/min with a starting dose of 900 mg/m^2. Treatment cycles were repeated every 2 weeks until disease progression or unacceptable toxicity occurred. Folic acid 350–1,000 μg/day orally and vitamin B_{12} 1,000 μg intramuscularly every 9 weeks were administered to all patients starting 1–2 weeks before the initiation of the first cycle of chemotherapy and continued until 3 weeks after the last dose of pemetrexed.

Dexamethasone 4 mg was given orally twice daily the day before, the day of, and for up to 2 days after pemetrexed infusion to prevent rash. Salicylates or other NSAIDs were interrupted for 2–5 days before and 2 days after pemetrexed infusion to avoid any interaction with renal function. Routine use of colony stimulating factor (CSF) was prohibited during the study. Granulocyte-CSF could be used in the setting of febrile neutropenia (defined as ANC <1,000/mm^3 with a fever >38.5°C) or grade 4 neutropenia lasting for more than 4 days. Other chemotherapeutic agents or investigational medications were not allowed.

Dose-limiting toxicity

Using the National Cancer Institute's Common Toxicity Criteria, version 2.0, DLT was defined as ≥1 of the following events that occurred during cycle 1 and required discontinuation or a significant dose reduction in the study drug(s): (1) grade 4 neutropenia (ANC < 500/mm^3) lasting for >5 days; (2) febrile neutropenia (ANC < 1,000/mm^3 with fever >38.5°C); (3) grade 4 thrombocytopenia (platelet count <25,000/mm^3); or (4) ≥grade 3 non-hematologic toxicity (excluding alopecia, nausea and vomiting, or grade 3 ALT or AST).

Dose escalation

Table 2 shows the dose-escalation schema, ranging from pemetrexed 300 mg/m^2 with gemcitabine 900 mg/m^2 over 90 min up to pemetrexed 800 mg/m^2 with gemcitabine 1,500 mg/m^2 over 150 min. No intra-patient dose escalation was allowed. At least 3 patients were enrolled at each dose level. If none of the first 3 patients experienced a DLT, then the next cohort of 3 patients were enrolled into the study and received the next dose level. The occurrence of 1 episode of DLT in the first 3 patients at any level required the accrual of 3 additional patients to that level. If no further episodes occurred, dose escalation proceeded. If 2 of 6 DLT episodes were identified, the given dose level was considered too toxic. At that time, 3 additional patients were entered at the previous dose level. If the previous dose level had 0/3 DLTs and no DLTs had been observed in the 3 additional patients (i.e., 0/6 DLTs), then this dose would be the recommended phase II dose. If the previous dose level had 1/6 DLTs and 0 or 1 DLTs were observed among the 3 additional patients (i.e., 1/9 or 2/9 DLTs, respectively), then this dose would be the recommended phase II dose. If there were 3 or more DLTs among 9 patients at this dose level, then the dose would be further de-escalated to

the prior level. The MTD was the dose at which 33% or more patients had DLTs. The recommended phase II dose would be the dose at which 0/6, 1/9, or 2/9 DLTs were observed.

Dose modifications

Patients experiencing DLT and failing to demonstrate benefit from therapy were removed from the study. However, if the investigator considered the patient to be benefiting from therapy, the patient could remain on study with dose adjustments. For ANC $\geq$500 and <1000 ($\times 10^6$/L) or platelets $\geq$50 and <100 ($\times 10^9$/L), pemetrexed and gemcitabine dose would be decreased by 25%. For ANC < 500 ($\times 10^6$/L) or platelets <50 ($\times 10^9$/L), treatment would be delayed for a week. If repeat of counts showed ANC $\geq$500 and platelets $\geq$50, then the patients were treated with the dose described above. Patient would be removed from the study for treatment delay >42 days. Any patient requiring dose reduction of either pemetrexed or gemcitabine would continue to receive a reduced dose for the remainder of the study. Any patient with 2 prior dose reductions who experienced a toxicity that would cause a third dose reduction would be withdrawn from study therapy. Treatment could be delayed for up to 42 days from Day 1 of the current cycle to allow a patient sufficient time to recover from toxicity. In addition to the dose-adjustment scheme for pemetrexed and gemcitabine as described above, pemetrexed dose was also adjusted based upon the severity of mucositis. Patients with grade 0–2 mucositis required no pemetrexed dose modification; grade 3–4 mucositis required a 50% dose reduction of pemetrexed. Any patient experiencing grade 3–4 recurrence of mucositis after 2 prior pemetrexed dose reductions was removed from study.

Pretreatment and follow-up studies

Patient histories, physical examinations, complete blood count with differential, serum electrolytes, and liver function tests were performed at baseline and before each course of treatment. Patients with measurable or evaluable disease were assessed with computed tomography or magnetic resonance imaging scans at baseline and after every 3 cycles of therapy to obtain response data. The indicator tumor could be a primary or metastatic lesion found on diagnostic imaging and tumor response was evaluated using the RECIST criteria. All objective responses were required to last for at least 4 weeks. All patients who were re-evaluated with scans after cycle 3 were evaluable for efficacy. Otherwise, they were considered inevaluable for response. Disease control rate (the percentage of patients with complete response (CR), partial response (PR) and SD) was added as a post hoc analysis for this report. All patients who receive at least 1 dose of pemetrexed and/or gemcitabine were evaluated for safety.

Results

Patient characteristics

Between October 2004 and January 2007, a total of 33 patients (21 male and 12 female) were enrolled. Patient characteristics are summarized in Table 1. The median age was 60 years (range: 21–82 years), and 100% of patients had an ECOG performance status of either 0 (33.3%) or 1(66.7%). The majority of patients were Caucasian (57.5%). Twenty patients (60.6%) had received prior

Table 1 Patient characteristics

Characteristics	Patients, *n*	%
Total patients	33	100.0
Sex		
Male	21	63.6
Female	12	36.4
Age (years)		
Median	60	
Range	21–82	
Race		
Asian	9	27.3
African American	2	6.1
Caucasian	19	57.5
Native Hawaiian or other Pacific islander	1	3.0
Unknown	2	6.1
ECOG performance score		
0	11	33.3
1	22	66.7
Prior chemotherapy		
1	20	60.6
2	11	33.3
Prior radiotherapy	9	27.3
Prior chemotherapy and radiotherapy	9	27.3
Disease site—pathology type		
Gastric adenocarcinoma	5	15.2
Pancreatic adenocarcinoma	5	15.2
Cholangiocarcinoma	5	15.2
Colon adenocarcinoma	3	9.1
Non-small-cell lung cancer	2	6.0
Hepatocellular carcinoma	2	6.0
Bladder carcinoma	2	6.0
Other	9	27.3

Includes all enrolled patients, including those who withdrew

ECOG Eastern Cooperative Oncology Group, *n* number

Table 2 Dose levels, course administered, and derived best response

Dose level	Pemetrexed[a] (mg/m^2)	FDR Gemcitabine[b]	*N*	Cycles received	Assessable patients, *n*	PR, *n*	SD, *n*	PD, *n*
1	300	900 mg/m^2 × 90 min	7	36	5	0	3	2
2	500	900 mg/m^2 × 90 min	3	23	2	0	2	0
3	500	1,200 mg/m^2 × 120 min	3	16	3	0	1	2
4	600	1,200 mg/m^2 × 120 min	3	22	3	0	3	0
5	700	1,200 mg/m^2 × 120 min	3	13	4	0	0	3
6	800	1,200 mg/m^2 × 120 min	9	68	7	2	3	3
7	800	1,500 mg/m^2 × 150 min	5	52	4	1	1	2
Total			33	230	28	3 (10%)	13 (46%)	12 (43%)

N number of patients, *n* number in group, *PD* disease progression, *PR* partial response, *SD* stable disease, *FDR* fixed-dose rate

[a] Infused over 10 min

[b] Fixed-dose rate infusion at 10 mg/m^2/min

chemotherapy, 11 patients (33.3%) had received 2 prior chemotherapy regimens, and 9 patients (27.3%) had received prior radiotherapy. All patients completed at least 1 cycle of pemetrexed and FDR gemcitabine therapy and therefore were assessable for toxicity; 28 patients were assessable for response. Gastrointestinal tumors were the most common tumor type: 6 patients had gastric adenocarcinoma, 5 had pancreatic adenocarcinoma, 5 had cholangiocarcinoma, 3 had colon cancer, 2 patients had NSCLC, 2 had hepatocellular carcinoma, 2 had bladder cancer, and the remainder had a variety of tumors.

Therapy administration

The patients treated on this study received a total of 230 cycles of therapy through 7 dose levels (see Table 2); the median number of cycles administered per patient was 4 (range, 1–35 cycles); 28 patients (84.8%) completed at least 3 cycles of therapy, 14 patients (42.4%) completed at least 6 cycles of therapy, and 7 patients (21.2%) completed at least 12 cycles of therapy. The causes of dose reductions were mainly febrile neutropenia and thrombocytopenia. The causes of cycle delays were neutropenia or febrile neutropenia.

Maximum tolerated dose and recommended dose

Dose-limiting toxicities occurred in 5 patients at dose levels 1, 6, and 7, although not all DLTs were drug-related. Febrile neutropenia was the principal DLT of this drug combination. Table 2 lists the number of patients enrolled at each dose level. The first patient treated at dose level 1 experienced acute renal failure secondary to dehydration and acute tubular necrosis, which was considered a DLT per protocol. Consequently, a fourth patient was added to dose level 1. This 83-year-old patient with pancreatic adenocarcinoma developed grade 3 febrile neutropenia with a concurrent perforated biliary stent infection with sepsis, and eventually died 2 days after treatment. The febrile neutropenia was determined to be a complication of the sepsis due to stent perforation, and thus not attributed to treatment. Subsequently, 4 additional patients were accrued at dose level 1; 3 of the additional patients were treated with no DLTs, and 1 patient was removed from the study prior to treatment for a total of 7 patients included at dose level 1. Since only 1 out of 7 patients enrolled at dose level 1 developed a DLT, dose escalation was continued with 3 patients enrolled per dose level and no DLTs were observed until dose level 6. One out of the first 3 patients at dose level 6 experienced febrile neutropenia (a DLT); dose level 6 was therefore expanded with 3 additional patients. Since there were no additional DLTs in dose level 6, dose escalation continued to dose level 7. The first patient at dose level 7 experienced a DLT with grade 4 febrile neutropenia associated with grade 3 infection (*Escherichia coli* sepsis) during the first cycle. Consequently, dose level 7 was expanded by 3 more patients (1 patient was removed prior to treatment) and 1 of the 2 additional patients experienced grade 3 febrile neutropenia. With two DLTs of 5 treated patients at dose level 7, three additional patients were enrolled at dose level 6, per protocol, for a total of 9 patients. No additional DLTs were observed at dose level 6. Therefore, dose level 7 (pemetrexed 800 mg/m^2 and FDR gemcitabine 1,500 mg/m^2) was designated as the MTD. The recommended phase II dose, defined prospectively as the next lower dose level from MTD, was therefore pemetrexed 800 mg/m^2 and FDR gemcitabine 1,200 mg/m^2 over 120 min.

Toxicity

All 33 patients were assessable for toxicity. Hematologic toxicities were observed at all dose levels of the study (Table 3). Overall, there were 3 patients who developed grade 3-4 neutropenia (9%), 1 patient with grade 4 thrombocytopenia (3%) and 3 patients with grade 3-4 anemia (9%).

Grade 3 febrile neutropenia and grade 3-4 hyperglycemia were the main non-hematologic toxicities noted. Hyperglycemia was due to dexamethasone premedication the day prior to treatment. Grade 3 (non-dose-limiting)

Table 3 Severity and frequency of hematologic toxicities by NCI-CTC grade at different dosing level

Toxicity	Neutropenia				Thrombocytopenia				Anemia		
Grade (*n*)	1	2	3	4	1	2	3	4	1	2	3
DL 1 (7)	–	–	–	–	2	–	–	–	2	3	–
DL 2 (3)	–	–	–	–	–	–	–	1	2	1	–
DL 3 (3)	–	–	–	–	–	–	–	–	2	1	–
DL 4 (3)	1	–	1	–	–	–	–	–	1	–	1
DL 5 (3)	–	–	–	1	–	1	–	–	3	1	–
DL 6 (9)	2	–	1	–	1	1	–	–	2	4	–
DL 7 (5)	–	1	–	–	1	–	–	–	1	–	2
Total (33)	3	1	2	1	4	2	0	1	13	10	3

DL dose level, *n* number of patients, *NCI-CTC* National Cancer Institute-Common Toxicity Criteria

fatigue was also observed at dose levels 6 and 7. Other non-hematologic toxicities included alopecia, skin rash, pruritis, muscle weakness, elevated alkaline phosphatase, dizziness, depression, and abdominal pain.

Antitumor activity

Although assessment of tumor response was not a primary objective of this phase I study, patients with measurable disease were evaluated for tumor response every 3 cycles (6 weeks) during treatment. One patient died from stent perforation (discussed previously), two patients withdrew consent, and two discontinued therapy before the first restaging. Twenty-eight of the 33 patients enrolled in the study were assessable for response. There were no patients experiencing CR. Three patients (1 each cholangiocarcinoma, bladder cancer, and pancreatic neuroendocrine tumor) had PRs (at dose levels 6 and 7), resulting in a response rate of 10.7%. Thirteen patients (46.4%; 3 with cholangiocarcinoma; 2 each with gastric carcinoma, NSCLC, and hepatocellular carcinoma; and 1 each with pancreatic adenocarcinoma, gastroesophageal junction adenocarcinoma, squamous cell carcinoma of the oral cavity, and nasopharyngeal carcinoma) were found to have confirmed stable disease on subsequent scanning. The overall disease control rate reached 57.1% in this mixed population of solid tumors, with 61% of patients having received previous chemotherapy in the metastatic setting and 36% of patients having received 2 prior chemotherapy regimens (Table 2). Six patients had prolonged SD (6 months or longer). One patient with NSCLC maintained SD for 17 months. Given the heterogeneous nature of non-disease-specific phase I study and the mixed patient population, caution should to be taken in interpretation of these data.

Discussion

Gemcitabine is most commonly administered as a weekly 30-min infusion for 3 consecutive weeks followed by a 1-week treatment break. Maximizing formation of the gemcitabine active metabolites by slowing the infusion rate to 10 mg/m^2/min to match activity of rate-limiting deoxycytidine kinase, has been previously demonstrated to be clinically feasible [2, 3]. FDR gemcitabine infusion has been adopted and applied in different phase II and III studies as either a single agent or in combination with other agents. The largest such study was a phase III trial in patients with advanced pancreatic cancer (E6201) [6], which demonstrated an equivalent overall survival for treatment with standard administration of gemcitabine, FDR gemcitabine alone (1,500 mg/m^2 × 150 min), and GEM-OX using FDR gemcitabine 1,000 mg/m^2. Both of the experimental regimens showed a tendency toward improved outcome when compared to standard gemcitabine dosing (1,000 mg/m^2 × 30 min), but neither arm met the statistical test required in the study design ($P < 0.025$). Toxicity, mainly hematologic, was only mildly increased in the experimental arms.

The current study was started before the definitve E6201 trial was reported and examined the MTD and DLTs of biweekly pemetrexed in combination with FDR gemcitabine. The recommended phase II doses were found to be pemetrexed 800 mg/m^2 and gemcitabine 1,200 mg/m^2 given at 10 mg/m^2/min. This dose intensity compares favorably to the single-agent recommendation of pemetrexed 500 mg/m^2 every 3 weeks in approved indications. When compared to a phase I study limited to patients with biliary tract or gallbladder carcinoma, which established an MTD of pemetrexed 500 mg/m^2 and gemcitabine 800 mg/m^2 over 80 min biweekly [21], our doses of FDR gemcitabine and pemetrexed were higher.

One possible explanation for the different doses found may be the fact that the presence of liver dysfunction limited a higher MTD in the patients with primary lesions in the biliary tract or gallbladder. Because we included a broad range of solid tumors in our trial, there appeared to be a better tolerance to higher dosing. Similar to our study, hematologic toxicities and hyperglycemia (related to steroid premedication) were the most common events seen [21].

Other studies have examined the combination of pemetrexed and bolus gemcitabine given in a variety of schedules and recommended day 8 administration of pemetrexed based on better hematologic tolerance [22]. While the Day 8 pemetrexed schedule, was carried forward into a large, randomized phase III trial in pancreatic cancer, and did not show a benefit over gemcitabine alone, the experience here also differed in using fixed dosing of gemcitabine and a more convenient schedule with concurrent administration every 2 weeks [15]. Another phase I dose-escalation study of biweekly pemetrexed with bolus gemcitabine in patients with solid tumors identified the MTD as 450 mg/m^2 for pemetrexed and 1,750 mg/m^2 for gemcitabine [23].

In the present study, pemetrexed and gemcitabine were combined on a biweekly basis in an effort to improve the toxicity profile while maintaining the dose intensity of the regimen. Although grade 4 neutropenia and febrile neutropenia were defined as DLTs, severe (grade 3–4) neutropenia occurred in only 9% of patients. The most common severe non-hematologic toxicity was hyperglycemia, which occurred in 8 patients (24%) and can be attributed to the use of dexamethasone premedication with pemetrexed. These findings indicate that the toxicity profile of biweekly pemetrexed/FDR-gemcitabine in our study of heavily pretreated patients with a mixed type of solid tumors was favorable and allowed delivery of higher dose intensity.

The combination of pemetrexed and gemcitabine is a promising chemotherapy regimen against a broad spectrum of solid tumors [24]. In the current study, 1 patient with NSCLC maintained SD for 17 months. Furthermore, prolonged stabilization of disease (>6 months) occurred in 6 patients. In addition, 3 PRs and 11 patients with confirmed stable disease were observed in a variety of GI and other cancers. Of particular note was 1 PR and 3 stable disease observed in cholangiocarcinoma out of 5 with this diagnosis enrolled. In a phase I study evaluating a mixture of tumor types at different dosing levels, it is difficult to define the clinical activity of an investigational combination chemotherapy regimen of two active agents. However, the frequency of disease stabilization across a broad range of tumor types, including several upper gastrointestinal cancers, suggests that this regimen should be further studied in phase II trials. The recommended phase II dose and schedule is pemetrexed 800 mg/m^2 and FDR gemcitabine 1,200 mg/m^2 over 120 min every 2 weeks.

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