A Phase I Trial of Pemetrexed Plus Gemcitabine Given Biweekly with B-Vitamin Support in Solid Tumor Malignancies or Advanced Epithelial Ovarian Cancer

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Abstract

Purpose: To determine the maximally tolerated dose (MTD) of biweekly pemetrexed with gemcitabine plus B_{12} and folate supplementation in patients with advanced solid tumors and ovarian cancer.

Experimental Design: Patients with no prior pemetrexed or gemcitabine therapy enrolled in cohorts of three, expanding to six if dose-limiting toxicity (DLT) was observed. Pemetrexed, escalated from to 700 mg/m^2, was given before gemcitabine 1,500 mg/m^2 every 14 days. DLTs were grade 4 neutropenia lasting >7 days or febrile neutropenia, grade 4 or 3 thrombocytopenia (with bleeding), grade ≥3 nonhematologic toxicity, or treatment delay of ≥1 week due to unresolved toxicity.

Results: The ovarian cancer cohort enrolled 24 patients with unlimited prior cytotoxic chemotherapies. MTD was observed at pemetrexed 600 mg/m^2, with 2 of 9 patients experiencing DLT. Most common grade 3 to 4 toxicities per patient were neutropenia (83%), leukopenia (67%), lymphopenia (73%), and febrile neutropenia (12%). Median cycle per patient was 8 (range, 1-16). Six of 21 (28%) patients had confirmed partial responses. Study protocol was modified for the solid tumor cohort (n = 30) to enroll patients with two or more prior cytotoxic regimens. MTD was observed at pemetrexed 500 mg/m^2, with 1 of 9 patients experiencing DLT. Most common grade 3 to 4 toxicities per patient were neutropenia (63%), lymphopenia (43%), leukopenia (70%) and febrile neutropenia (6.6%). Median cycle per patient was 4 (range, 1-20). Three of 29 (10.3%) response-evaluable patients had confirmed partial responses: 2 squamous cell carcinomas of head and neck and 1 nasopharyngeal cancer.

Conclusion: MTDs for the solid tumor and ovarian cancer cohorts were reached at pemetrexed 500 and 600 mg/m^2, respectively, given biweekly with gemcitabine 1,500 mg/m^2.

New treatments for patients with advanced solid tumors are needed. Pemetrexed is a multitargeted antifolate cytotoxic agent with activity in mesothelioma (1), non-small cell lung cancer (2), and other solid tumors. Folate receptors, which are expressed at high levels on the surface of ovarian cancer cells, may provide excellent targets for pemetrexed. Single-agent gemcitabine has activity in platinum-resistant epithelial ovarian cancer (3), pancreatic cancer (4), lung cancer, and other solid tumors (5). Preclinical data have shown synergistic effects of pemetrexed combined with gemcitabine (6, 7). Both pemetrexed and gemcitabine cause myelosuppression, which may limit drug delivery. However, granulocyte nadirs generally occur between days 6 and 10 for both agents, making a biweekly schedule potentially easier to deliver. Folic acid and vitamin B_{12} supplementation permits higher doses of pemetrexed to be delivered with acceptable toxicity (1, 8). We designed this phase I study to determine whether every 14-day (biweekly) dosing, coupled with B-vitamin support, would permit potentially efficacious doses of pemetrexed to be delivered in combination with full-dose gemcitabine. Pemetrexed was infused before gemcitabine based on previous work showing that the pemetrexed followed by gemcitabine sequence appeared to be less toxic compared with the treatment schedules in which gemcitabine was given before pemetrexed (9).

The optimal dose and schedule of pemetrexed plus gemcitabine with B-vitamin support has not been defined. Based on reported experiences with gemcitabine dosing in ovarian cancer patients (10, 11), we postulated that ovarian cancer patients and other solid tumor patients might differ in their tolerability for this cytotoxic combination and thus aimed to define the maximally tolerated dose (MTD) in two separate patient groups. We excluded patients with prior treatment with

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Table 1. Number of prior cytotoxic therapies and prior radiation history for patients enrolled in the solid tumor cohort (n = 30)

Dose level	Histology/tumor type	No. prior cytotoxic therapies	Prior radiation therapy history	No. cycles of study treatment
1	Invasive ductal carcinoma-breast	3	Breast, supraclavicular fossa, whole brain radiation	4
1	Head and neck carcinoma	3	Mandible, neck, parapharyngeal space	20
1	Neuroendocrine carcinoma of the vulva	3	Left labia majora	1
2	Soft-tissue sarcoma of the thigh-pleomorphic liposarcoma	2	Left thigh	1
2	Non-small cell lung cancer	1	None	3
2	Non-small cell lung cancer	1	None	14
2	Renal cell carcinoma-clear cell	3	Whole-brain radiation	2
2	Colon cancer	5	Hip and femur	3
2	Colon cancer	3	None	2
2	Head and neck, squamous cell carcinoma	2	Thoracic spine (T3-T7)	16
2*	Nasopharyngeal carcinoma	2	Nasopharynx, supraclavicular lymph nodes, posterior neck	8
2*	Nasopharyngeal carcinoma	1	Nasopharynx	20
2*	Rectal cancer-squamous cell carcinoma	2	Right pubic ramus	1
2*	Atypical carcinoid arising from the trachea	2	Neck	4
2*	Head and neck, squamous cell carcinoma	1	Larynx and lymph nodes	3
2*	Nasopharyngeal carcinoma	1	Nasopharynx, supraclavicular lymph nodes, posterior neck	16
2*	Head and neck, squamous cell carcinoma	2	Breast, oral cavity, neck	4
2*	Nasopharyngeal carcinoma	2	Nasopharynx, supraclavicular lymph nodes, posterior neck	3
3	Non-small cell lung cancer	1	None	6
3	Non-small cell lung cancer	1	None	15
3	Head and neck, squamous cell carcinoma	2	None	8
4	Head and neck, squamous cell carcinoma	1	Head and neck radiation	4
4	Head and neck, squamous cell carcinoma	2	Head and neck radiation	4
4	Head and neck, squamous cell carcinoma	1	Head and neck radiation	12
3	Thyroid cancer	1	Thyroid/neck radiation	11
3	Carcinosarcoma of the ovary	2	None	2
3	Endometrial adenocarcinoma	1	None	7
3	Uterine carcinosarcoma	1	None	8
3	Endometrial adenocarcinoma	2	None	2
3	Non-small cell lung cancer	3	None	8

*After DLT was observed at dose level 2, the protocol eligibility criteria were amended to permit solid tumor patients with no more than two prior cytotoxic treatments and no history of whole brain radiation, and dose level 2 was repeated with patients meeting these stricter eligibility criteria.

pemetrexed or gemcitabine to evaluate whether there was preliminary evidence of antitumor activity of this regimen as measured by objective response.

Materials and Methods

Patients. Patients were accrued in two independent cohorts: patients with ovarian cancer and patients with other solid tumors. Patients were eligible if they met the following criteria: histologic or cytologic diagnosis of solid tumor malignancy or ovarian cancer not considered curable by standard treatments; no prior treatment with pemetrexed or gemcitabine; age ≥18 years; Zubrod performance status 0 or 1; at least 2 weeks from prior radiation and recovered from toxicities of prior treatment; absolute neutrophil count ≥1,500/μL; platelet count ≥100,000/μL; hemoglobin ≥9 g/dL; bilirubin ≤1.5 × upper limit of normal; alkaline phosphatase, aspartate transaminase, and alanine transaminase ≤3 × upper limit of normal, unless there was liver involvement by tumor, in which case ≤5 × upper limit of normal was acceptable; calculated creatinine clearance ≥45 mL/min using Cockroft and Gault formula; negative pregnancy test for patients of child-bearing potential; and estimated life expectancy of ≥12 weeks. Patients with prior radiation to <25% of the bone marrow were eligible, but patients with prior whole-pelvic or whole-brain radiation were excluded. Patients with ovarian cancer were permitted to have an unlimited number of prior cytotoxic chemotherapy regimens. Patients with advanced solid tumors were initially permitted to have an unlimited number of prior chemotherapies, but after two dose-limiting toxicities (DLT) were observed in solid tumor dosing cohort 2, this eligibility criterion was amended to permit only up to two prior cytotoxic regimens for patients in the solid tumor group. Patients were excluded for prior experimental therapy in the 30 days before enrollment, pregnancy, or breast-feeding, serious systemic disorder or active infection, history of brain metastases, and inability to take B_{12} and folate supplementation or dexamethasone.

Concomitant treatment. Patients were required to interrupt use of aspirin or other nonsteroidal anti-inflammatory medication for at least 5 days before any treatment day to limit any effects on pemetrexed clearance (12). All patients received vitamin B_{12} 1,000 μg intramuscularly 1 to 2 weeks before first dose of pemetrexed and then approximately every 9 weeks while on study treatment and until 3 weeks

Table 2. Summary of solid tumor dosing cohorts and DLT events

Level	Gemcitabine dose (mg/m^2)	Pemetrexed dose (mg/m^2)	Patients (*n*)	DLT event detail
1	1,500	300	3	No DLT-evaluable patients experienced DLT
2	1,500	400	7	2 of 6 DLT-evaluable patients experienced DLT Grade 3 thrombocytopenia, failure to recover ≤1 wk Febrile neutropenia
2*	1,500	400	8	1 of 6 DLT-evaluable patients experienced DLT Grade 3 thrombocytopenia, failure to recover ≤1 wk
3	1,500	500	9	1 of 9 DLT-evaluable patients experienced DLT Febrile neutropenia
4	1,500	600	3	2 of 3 DLT-evaluable patients experienced DLT Grade 4 hyponatremia Grade 2 herpes zoster infection, failure to resolve ≤1 wk

After the initial cohort treated at dose level 2, the protocol was amended to limit enrollment to patients with ≤2 prior regimens of cytotoxic chemotherapy and to exclude patients with prior whole-brain radiation therapy. Treatment was continued starting at dose level 2. Although 8 patients were enrolled on dose level 2, 2 patients were replaced in that cohort because they were not considered evaluable for DLT. Please see text for details.

after discontinuation of study treatment. All patients received daily oral folic acid 350 to 1,000 μg, starting 1 to 2 weeks before first dose of pemetrexed. Dexamethasone 4 mg by mouth twice daily was given the day before, the day of, and the day after each study treatment to diminish the risk of rash associated with pemetrexed.

Routine use of granulocyte colony-stimulating factors was not permitted. Granulocyte colony-stimulating factor was permitted for treatment of patients with documented absolute neutrophil count <500/μL, neutropenic fever, or documented infection while neutropenic. If given, granulocyte colony-stimulating factor had to be discontinued ≥24 h before study treatment. Erythropoietin-stimulating agents were permitted.

Pemetrexed and gemcitabine dosing. On day 1 of each 14-day cycle, pemetrexed was given by intravenous infusion according to the assigned dosing cohort over ~10 min followed immediately by intravenous infusion of gemcitabine 1,500 mg/m^2 over ~30 min. The next cycle of treatment was delivered on time provided that the following criteria were met: absolute neutrophil count ≥1,000/μL, platelets ≥100,000/μL, no mucositis worse than grade 2, no treatment-related pulmonary toxicity worse than grade 1, calculated creatinine clearance remained ≥45 mL/min, and no other grade 3 or worse nonhematologic toxicity remained unresolved. Grade 3 transaminase elevations did not require a dose delay. Treatment was delayed for up to 1 week if absolute neutrophil count or platelet count were too low for treatment. If counts recovered within 1 week, treatment resumed at the same dose.

Patients with grade ≥3 diarrhea could resume therapy at 75% of the prior dose once diarrhea had resolved to baseline. Patients with grade 3 or 4 mucositis were permitted to resume therapy at 75% and 50% of the prior dose, respectively. Treatment delays of up to 28 days (35 days for decreases in creatinine clearance) were permitted to allow resolution of toxicity. If treatment was resumed, doses were reduced to 75% of prior dose. If toxicity had not resolved to a level to permit retreatment, the patient was removed from study. Patients with grade 2 or worse treatment-related pulmonary toxicity were removed from study regardless of whether toxicity resolved. Patients who continued to experience toxicity despite two dose reductions were removed from study treatment. All patients had complete blood counts done weekly to assess for hematologic toxicity.

Treatment dose levels were as follows: dose level 1: pemetrexed 300 mg/m^2 plus gemcitabine 1,500 mg/m^2, dose level 2: pemetrexed 400 mg/m^2 plus gemcitabine 1,500 mg/m^2, dose level 3: pemetrexed 500 mg/m^2 plus gemcitabine 1,500 mg/m^2, dose level 4: pemetrexed 600 mg/m^2 plus gemcitabine 1,500 mg/m^2, and dose level 5: pemetrexed 700 mg/m^2 plus gemcitabine 1,500 mg/m^2.

Statistical design. The primary outcome of the study was the determination of MTD of biweekly gemcitabine plus pemetrexed among patients with ovary cancer who had had an unlimited number of prior cytotoxic therapies and the determination of MTD among patients with other solid tumors who had had no more than two prior cytotoxic regimens.

Patients were enrolled in dose level groups of three, with separate, parallel cohorts for patients with ovarian cancer and for patients with other solid tumors. If none of the 3 patients at any dose level experienced a DLT within the first four cycles of treatment, the dose level was escalated to the next dose level. If 1 of 3 patients experienced a DLT, up to 3 more patients were treated at that dose level for a total of 6 patients. If no more than 1 of these 6 patients experienced a DLT, the dose level was escalated to the next dose level. If ≥2 of the 6 patients experienced a DLT, that dose level was considered not tolerable. Then, the preceding dose level was expanded to include a total of 9 patients. The MTD was defined as the dose level at which DLTs were observed in no more than 2 of 9 patients. Per protocol, all 9 patients must have received at least 4 cycles of study treatment; however, if a DLT occured before cycle 4, that DLT counted. Patients who discontinued the study after only one cycle of treatment for reasons other than toxicity were replaced in the cohort for the purposes of MTD determination but were still considered assessable for response.

Table 3. Frequency of grades 3 and 4 toxicities, at least possibly related to study treatment, occurring during the first four cycles of study treatment, among patients in solid tumor cohort (*n* = 30)

Toxicity	Grade 3, *n* (%)	Grade 4, *n* (%)
Febrile neutropenia	1 (3)	1 (3)
Neutropenia	5 (17)	14 (47)
Lymphopenia	10 (33)	3 (10)
WBC count	15 (50)	6 (20)
Anemia	9 (30)	0
Thrombocytopenia	2 (7)	1 (3)
Aspartate transaminase or alanine transaminase elevation	8 (27)	1 (3)
Infection, without neutropenia	1 (3)	0
Hyponatremia	0	1 (3)
Edema	2 (7)	0

Table 4. Number of prior cytotoxic therapies, and prior radiation, received by patients enrolled in the ovarian cancer cohort (n = 24)

Dose level	Tumor type	No. prior cytotoxic therapies	Prior radiation therapy history	No. cycles of study treatment
1	Ovarian cancer	3	None	3
1	Ovarian cancer	3	None	1
1	Ovarian cancer	2	None	15
1	Ovarian cancer	3	None	4
2	Ovarian cancer	3	None	16
2	Ovarian cancer	1	None	3
2	Ovarian cancer	1	None	8
3	Ovarian cancer	2	None	9
3	Ovarian cancer	4	None	7
3	Ovarian cancer	2	None	4
3	Ovarian cancer	4	None	5
3	Ovarian cancer	2	None	8
3	Ovarian cancer	1	None	8
4	Ovarian cancer	3	None	16
4	Ovarian cancer	2	None	16
4	Ovarian cancer	2	None	4
4	Ovarian cancer	2	None	11
4	Ovarian cancer	6	None	9
4	Ovarian cancer	3	None	8
4	Ovarian cancer	2	None	12
4	Ovarian cancer	4	None	6
4	Ovarian cancer	3	None	9
5	Ovarian cancer	1	None	2
5	Ovarian cancer	1	None	1

Dose-limiting toxicity. DLT was defined as any of the following events: grade 4 neutropenia lasting >7 days or febrile neutropenia; grade 4 or 3 thrombocytopenia with bleeding; grade 3 or worse nonhematologic toxicity (excluding alopecia, nausea, and vomiting); or grade 3 elevated ALT or AST; and treatment delay of ≥1 week due to unresolved hematologic or nonhematologic toxicity. The period for observation of DLTs was defined as the first four cycles of therapy (~8 weeks).

Criteria for response. Objective response was assessed by computed tomography imaging done approximately every 8 weeks (each cycle was 2 weeks; thus, imaging was after every four cycles) using RECIST among patients with measurable disease, who had received at least one cycle of treatment. In the ovarian cancer cohort, patients whose platinum-free interval from last dose of platinum to documentation of tumor progression was under 6 months were considered to be platinum-resistant. Patients who had ≥50% decrease in the CA-125 level on two sequential measurements were considered to have had a CA-125 response.

Results

Solid tumor patient cohort

Determination of MTD. A total of 30 solid tumor patients enrolled. Details of each patient's number of prior cytotoxic therapies and prior radiation are shown in Table 1. Initially, solid tumor patients were permitted to have had an unlimited number of prior cytotoxic treatments and to have had prior whole-brain radiation. Three patients were treated at dose level 1 and none experienced DLT. A total of 7 patients were enrolled at dose level 2. The first patient received only one cycle of treatment and was removed from study for disease progression. Per protocol specifications, this patient was replaced in the cohort to provide sufficient treatment exposure for assessment of toxicity. Two of the additional 6 patients at dose level 2 experienced DLT (1 grade 3 thrombocytopenia with failure to recover within 1 week and 1 febrile neutropenia). The protocol was subsequently amended to limit the number of prior cytotoxic regimens to two and to exclude patients with prior whole-brain radiation. A total of 8 patients meeting these revised eligibility criteria were then treated at dose level 2, now called "2*." One patient was replaced in the cohort because she was removed from study for disease progression after only one cycle. An additional patient was replaced because the planned complete blood count analysis following cycle 4 was omitted, not allowing evaluation of absolute neutrophil count recovery. Of the 6 patients treated and completely evaluable for DLT, 1 experienced DLT (grade 3 thrombocytopenia with failure to recover within 1 week). Three patients were treated at dose level 3 with no DLTs observed. Three patients were treated at dose level 4, with 2 patients experiencing DLTs (grade 4 hyponatremia and grade 2 herpes zoster infection with failure to resolve within 1 week). Based on these observations, dose level escalation was stopped at dose level 4. Six additional patients were treated at dose level 3, for a total of 9 patients, 1 of which had a DLT (neutropenic fever). Thus, dose level 3, pemetrexed 500 mg/m^2 plus gemcitabine 1,500 mg/m^2, was determined as the MTD. A summary of dose levels and the frequencies and types of DLTs observed in the solid tumor cohort is provided in Table 2.

Toxicities, treatment duration, and response in solid tumor patients. Thirty solid tumor patients (median number of prior regimens, 2; range, 1-5; 63% of patients had had prior radiation) received a total of 212 cycles of study treatment. Frequencies of grade 3 and 4 toxicities considered at least possibly related to study treatment are shown per patient in Table 3. The median number of cycles delivered per patient was 4 (range, 1-20). Dose delays of ≥1 day were required in 23.3% of patients in the first four cycles. Three of 29 (10%) patients evaluable for response had objective partial response:

Table 5. Summary of ovarian cancer dosing cohorts and DLT events

Level	Gemcitabine dose (mg/m^2)	Pemetrexed dose (mg/m^2)	Patients (*n*)	DLT event detail
1	1,500	300	4*	No DLT-evaluable patients experienced DLT
2	1,500	400	3	No DLT-evaluable patients experienced DLT
3	1,500	500	6	1 of 6 DLT-evaluable patients experienced DLT Grade 3 thrombocytopenia, failure to recover ≤1 wk
4	1,500	600	9	2 of 9 DLT-evaluable patients experienced DLT 2 patients with febrile neutropenia
5	1,500	700	2	2 of 2 DLT-evaluable patients experienced DLT Febrile neutropenia Grade 3 rash

*One patient was removed from the dose level 1 cohort for probable disease progression and a fourth patient was added to meet protocol requirements for DLT assessment.

2 squamous cell carcinoma of head and neck and 1 nasopharyngeal cancer.

Ovarian cancer patient cohort

Determination of MTD. Twenty-four patients enrolled with a median of 2 prior regimens (range, 1-6). Details of number of prior cytotoxic therapies and prior radiation are given in Table 4. Four patients were treated at dose level 1, with 1 patient coming off study for probable progression after one cycle, necessitating replacement for determination of tolerability. Among the 3 patients receiving adequate therapy to be considered assessable for DLT, no DLTs were observed. Three patients were treated at dose level 2, with none experiencing DLT. Six patients were treated at dose level 3, with 1 of 6 experiencing a DLT (grade 3 thrombocytopenia, which required dose delay of >1 week to recover platelets to >100,000/μL to permit retreatment). Six patients were treated at dose level 4, with 1 of 6 experiencing DLT (neutropenic fever). Two patients were treated at dose level 5, with both patients experiencing DLT (1 neutropenic fever and 1 grade 3 rash). Dose level 4 was expanded to include 3 additional patients to bring the total number treated at that dose level to 9, with 2 of 9 experiencing DLT (both neutropenic fever). Thus, pemetrexed 600 mg/m^2 plus gemcitabine 1,500 mg/m^2 was determined as the MTD in ovarian cancer patients. A summary of dose levels, number of patients treated, and DLTs observed is provided in Table 5.

Toxicities, treatment duration, and response in ovarian cancer patients. Frequency of toxicities considered at least possibly related to study treatment are shown per patient in Table 6 for the ovarian cancer cohort. The most common grade 3 to 4 toxicities observed were neutropenia (50.8%), leukopenia (39.5%), lymphopenia (10.2%), and anemia (1.1%). Patients also experienced febrile neutropenia 1.6%, grade 3 thrombocytopenia (0.5%), grade 3 rash (0.5%), grade 3 infection (0.5%), and grade 3 dehydration (0.5%).

The median number of cycles delivered per patient was 8 (range, 1-16). Dose delays of ≥1 day to permit resolution of toxicity were required in 8.3% of patients in the first four cycles. Twenty-one of the 24 patients enrolled were considered evaluable for RECIST objective response (2 patients had no measurable disease and 1 patient received only one dose of treatment and came off study for grade 3 rash but had no evidence of disease progression). Nineteen of these 21 patients were considered platinum-resistant, with platinum-free intervals all less than 6 months. Confirmed partial response was observed in 6 of these 21 (28%) patients, all were platinum-resistant. CA-125 response, defined as a ≥50% decrease in serum CA-125 confirmed by two measurements, was observed in 13 of 24 (54%) patients.

Delayed toxicity. We observed grade 2 or 3 dizziness/ataxia in a total of 6 patients (Table 7). All patients had been on treatment for ≥6 cycles (range, 6-13); thus, these events were beyond the protocol-defined DLT observation period. All events were initially thought to be potentially treatment related. Four patients (2 ovarian cancer and 2 solid tumor) with grade 2 ataxia came off study. The symptoms resolved to grade 0 in all 4 patients after discontinuation of study treatment. One patient with grade 3 ataxia was removed from study treatment. Workup for other causes of ataxia was negative. Symptoms improved only to grade 2 and persisted at 7 months' follow-up since treatment discontinuation. The other patient with grade 3 ataxia initially had a negative workup for other causes of ataxia, but on follow-up imaging was found to have a new occipital brain metastasis, which was resected and confirmed to be

Table 6. Frequency of grades 3 and 4 toxicities, at least possibly related to study treatment, occurring during the first four cycles of study treatment, among patients in ovarian cancer cohort (*n* = 24)

Toxicity	Grade 3, *n* (%)	Grade 4, *n* (%)
Febrile neutropenia	1 (4)	1 (4)
Neutropenia	4 (17)	17 (71)
Lymphopenia	9 (38)	0
WBC count	13 (54)	4 (17)
Anemia	3 (13)	0
Thrombocytopenia	0	0
Rash/desquamation	1 (4)	0
Dehydration	1 (4)	0
Infection, without neutropenia	1 (4)	0
International normalized ratio	1 (4)	0

ovarian cancer. This ataxia event was subsequently deemed unrelated to study treatment. At the time that these events were noted, the institutional review board was notified and accrual was halted pending review of these toxicities. The informed consent was amended to include dizziness/ataxia as a possible toxicity of treatment. In summary, there were four grade 2 dizziness/ataxia events that were probably treatment-related and resolved with treatment discontinuation, one grade 3 ataxia that improved only to grade 2, and one grade 3 event subsequently deemed unrelated to study treatment.

Discussion

This study defined the MTD of biweekly pemetrexed plus gemcitabine with B-vitamin support in two separate patient populations: patients with advanced solid tumors and no more than two prior cytotoxic regimens and patients with advanced ovarian cancer and an unlimited number of prior cytotoxic regimens. The MTD was slightly higher (pemetrexed 600 mg/m^2 + gemcitabine 1,500 mg/m^2) in the ovarian cancer cohort than in the solid tumor cohort (pemetrexed 500 mg/m^2 + gemcitabine 1,500 mg/m^2). DLT in both cohorts was largely attributable to myelosuppression.

Other doses and schedules of pemetrexed and gemcitabine have been studied in various patient populations. A phase I study of biweekly treatment was conducted in patients with solid tumors with starting doses of gemcitabine 1,250 mg/m^2 plus pemetrexed 300 mg/m^2. All patients received vitamin B_{12} and folate supplementation. Sixty-six percent of patients had received two or more chemotherapy regimens before enrollment. The MTD in that trial was gemcitabine 1,750 mg/m^2 plus pemetrexed 450 mg/m^2, with DLTs related to myelosuppression (13). These results are consistent with the MTDs and toxicity profiles defined in solid tumor and the ovarian cancer cohorts treated in the phase I study reported here.

A randomized phase II trial evaluated toxicity and response rates among three different sequences of pemetrexed plus gemcitabine on days 1 and 8 of a 21-day schedule, given to chemotherapy-naive non-small-cell lung cancer patients. In all three arms, drug delivery was separated by a 90-min interval (9). This phase II study showed that pemetrexed followed by gemcitabine appeared to be less toxic and achieved a higher response rate compared with the other treatment schedules in which gemcitabine was given before pemetrexed. With pemetrexed followed by gemcitabine on day 1 and gemcitabine alone on day 8 of a 21-day cycle, grades 3 and 4 neutropenia was observed in 64% of patients and grades 3 and 4 thrombocytopenia in 8.5%. In contrast, our study of pemetrexed followed by gemcitabine with no treatment time interval and with both drugs delivered biweekly to a patient population with a median of two prior regimens showed an incidence of grades 3 and 4 neutropenia of 38.1% in the solid tumor cohort and 50.8% in the ovarian cohort. The frequency of grades 3 and 4 thrombocytopenia was 1.9% in the solid tumor cohort and 0.5% in the ovarian cohort.

Further data regarding myelosuppression from gemcitabine plus pemetrexed administered on a 21-day schedule come from a phase III trial in pancreatic cancer patients with no prior cytotoxic therapy. In the gemcitabine-pemetrexed arm, gemcitabine 1,250 mg/m^2 was given days 1 and 8 with pemetrexed 500 mg/m^2 following gemcitabine on day 8 of a 21-day cycle. With these doses and schedule, grades 3 and 4 neutropenia occurred in 45% of patients, grades 3 and 4 thrombocytopenia in 17.9%, and febrile neutropenia in 9.9% (14).

Our results appear to support the hypothesis that biweekly dosing of pemetrexed followed by gemcitabine may be more tolerable than a 21-day dosing schedule. A preliminary report of a phase I study of similar design to ours (biweekly pemetrexed followed by gemcitabine with B-vitamin support in solid tumor patients) defined the MTD as pemetrexed 500 mg/m^2 and gemcitabine 1,500 mg/m^2, which is similar to the MTDs established for the solid tumor and ovarian cancer cohorts of our study (15).

Gemcitabine is considered active as a single agent in platinum-resistant ovarian cancer, although objective response rates are relatively low: 6.1% in a recent phase III trial comparing gemcitabine with pegylated liposomal doxorubicin (3). In our phase I study of pemetrexed plus gemcitabine, 28% of patients with relapsed ovarian cancer had objective responses, with all responses observed in platinum-resistant patients. This objective response rate appears promising for this combination in ovarian cancer. Results of phase II studies of single-agent pemetrexed in platinum-resistant ovarian cancer are expected (16, 17). The observation of two objective responses in head and neck cancer patients and one in nasopharyngeal cancer merits further investigation of this combination in these tumor types.

The toxicities observed in this phase I study were mostly related to myelosuppression, which was the expected toxicity profile for these agents. The five delayed grade 2 and 3 dizziness/ataxia toxicity events considered possibly related to drug treatment merit further consideration. Although such events have not been reported with other phase I trials studying pemetrexed and gemcitabine combination therapy at other doses and schedules, it may be that these ataxia events only occur with more prolonged therapy. Because many patients in

Table 7. Summary of patients with ataxia-dizziness delayed toxicity events (n = 5)

Patient	Age	Disease	Dose level	No. cycles received before toxicity	Ataxia/ dizziness grade	Outcome
1	43	Ovary	4	13	2	Resolved to grade 0 off study treatment
2	53	Ovary	4	6	2	Resolved to grade 0 off study treatment
3	63	Head and neck	4	12	2	Resolved to grade 0 off study treatment
4	69	Endometrial	3	7	3	Further evaluation detected brain metastases; ataxia event deemed unrelated to study treatment
5	74	Ovary	4	9	3	Symptoms improved to grade 2 off study treatment
6	65	Anaplastic thyroid	3	10	2	Resolved to grade 0 off study treatment

both the solid tumor and the ovarian cancer cohorts were able to remain on study for longer than six cycles (12 weeks), we may have had a greater opportunity to observe potential late toxicities.

In summary, the MTD of biweekly pemetrexed plus gemcitabine is 500 and 1,500 mg/m^2 among patients with solid tumor malignancies and up to two prior cytotoxic therapies and 600 plus 1,500 mg/m^2 among women with advanced epithelial ovarian cancer and an unlimited number of prior cytotoxic regimens. The high objective response rate among patients with platinum-resistant ovarian cancer merits further study.

Disclosure of Potential Conflicts of Interest

F. Tai, M. Orlando, and T. Goss are employed by Lilly. M. Hensley has received research funding from Lilly. P. Sabbatini is on the Lilly speakers' bureau.

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