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ORIGINAL ARTICLE

A phase II study of biweekly pemetrexed and gemcitabine in patients with metastatic breast cancer

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Abstract
Purpose Pemetrexed (PEM) is a novel folate antimetabolite which inhibits thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyl transferase. This phase II study was designed to assess the efficacy of Gemcitabine (GEM) and PEM given in a novel schedule in metastatic breast cancer (MBC) patients.
Methods Eligible patients had MBC and received one prior chemotherapy regimen for metastatic disease; Performance status (PS) 0–2; measurable disease (RECIST criteria). PEM(500 mg/m^2) was administered intravenously (IV) over 10 min prior to GEM(1,500 mg/m^2) IV given over 30 min on day 1 every 14 days.
Results Median age of the 16 patients in the study was 54 years (range 33–77). Fourteen patients had a PS of 0/1 and were evaluable for response. There were no reported complete or partial responses, seven patients with stable disease, six patients with disease progression and one patient with unknown response. Most common toxicities were skin rash: Grade 1/2(8) and Grade 3/4(1). Grade 3/4 non-hematological toxicities were fatigue(1); anorexia(1); pneumonia(1); peripheral ischemia(1) and elevation of liver transaminases(1). Three patients experienced febrile neutropenia (FN). This study did not meet the predefined criteria to proceed with additional accrual.
Conclusions This regimen of PEM and GEM showed no clinical activity in the dose and schedule tested.

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Abbreviations

CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
DHFR	Dihydrofolate reductase
ECOG	Eastern Cooperative Oncology Group
FEC	Anthracycline based combination therapy
FN	Febrile neutropenia
GARFT	Glycinamide ribonucleotide formyl transferase
GEM	Gemcitabine
GET	Gemcitabine combination therapy
HER-2	Human epidermal growth factor receptor-2
IHC	Immuno histo chemistry
LY231514	Pemetrexed, ALIMTA, multitargeted antifolate
MBC	Metastatic breast cancer
NSCLC	Non-small cell lung cancer
PEM	Pemetrexed
PS	Performance status
RECIST	Response evaluation criteria in solid tumors
TS	Thymidylate synthase

Introduction

Breast cancer is the most common malignancy that affects women in the western world, and is the second most common cause of cancer-related death in women in Canada [1]. Despite advances in detection, treatment and prevention, many women will develop metastatic breast cancer (MBC) with a median survival of 2–3 years.

Pemetrexed (PEM) is a novel folate antimetabolite, which inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT) [2–4]. A number of studies have shown PEM to be active as a single agent in women with MBC with reported objective response rates of 8% [5] (heavily pretreated patients) to 28% [6]. Single agent gemcitabine (GEM) has activity in women with MBC with response rates ranging from 0 to 40% [7].

Pre-clinical data of the combination of PEM and GEM has demonstrated synergistic activity [8–12]. However, there remains uncertainty about the optimal schedule of administration of these two agents, with some studies suggesting greater activity when GEM is preceded by a thymidylate synthetase inhibitor [8–10]. Other studies showed increased activity with the reverse order of administration [11, 12]. A Phase I study at the Mayo Clinic investigated the combination of PEM and GEM administered in 21-day cycles [11] and revealed promising clinical activity in a variety of solid tumors with a response noted in one patient with breast cancer. A subsequent study in breast cancer patients using a three-week schedule of PEM and GEM reported a 24% response rate [13].

Recently, investigators have explored alternate schedules of drug administration in an effort to increase overall drug exposure with the ultimate goal of increasing the efficacy of therapy. At the time this study commenced, investigators were examining an every other week schedule of PEM and GEM. Such a program increases the amount of PEM delivered over a 6-week interval by 50% while at the same time keeping the dose of GEM within the range of delivered doses (90–112%). Phase I/II studies using this treatment schedule have been reported since this trial began and both reported activity meriting further evaluation [14, 15].

We report on an open label phase II study of biweekly PEM and GEM in patients with MBC.

Materials and methods

Study design

This was an open label, single-arm phase II trial conducted at The Ottawa Hospital Cancer Centre. The primary objective was to determine the overall response rate for PEM plus GEM administered every 14 days, in patients with MBC who had received up to one prior chemotherapy regimen for metastatic disease. Secondary objectives included: time to objective tumor response, duration of response, time to treatment failure, time to progressive disease, progression-free survival and overall survival. The quantitative and qualitative toxicities of PEM plus GEM in this patient population were also explored.

Patient population

Patients were eligible if they had MBC with at least one unidimensionally measurable lesion by RECIST criteria (Response evaluation criteria In solid tumors) [16], Eastern Cooperative Oncology Group performance status of 0–2, and were 18 years of age or older. No more than one prior chemotherapy regimen for metastatic disease was allowed. Prior hormonal therapy was permitted as was adjuvant chemotherapy provided it was completed at least 1 year prior to the development of metastatic disease. Radiation therapy had to be completed at least 4 weeks before study enrollment. Exclusion criteria included: pregnant or lactating women, patients with symptomatic brain metastases, previous treatment with GEM, or clinically relevant third space fluid collections. Patients with other malignancies who were cured and had completed all therapies at least 5 years prior to the study were eligible. The study was conducted in accordance with the Declaration of Helsinki and approved by The Ottawa Hospital Research Ethics Board. Written, informed consent was obtained from all patients.

Study treatment

All patients received folic acid (350–600 μg daily) and vitamin B_{12} (1,000 μg intramuscular every 9 weeks) 1–2 weeks prior to initiation of chemotherapy, and dexamethasone (4 mg) twice daily for 3 days starting 24 h prior to chemotherapy treatment. All patients received PEM (500 mg/m^2 IV infusion, given over 10 min) on Day 1 of chemotherapy treatment immediately prior to GEM infusion (1,500 mg/m^2 IV infusion, given over 30 min). PEM was supplied by Eli Lilly Canada (Toronto, Ontario). Patients continued treatment with biweekly PEM and GEM for 12 treatments (12 cycles): until disease progression, occurrence of unacceptable toxicity, or patient's decision.

Patients were evaluated for toxicity prior to each cycle using the Common Terminology Criteria for adverse event (CTCAE: version 3.0). Response and progression were evaluated using RECIST [16]. All patients who received at least one cycle of therapy were evaluable for response and toxicity. Patients coming off study prior to disease progression were followed every 8 weeks. Any toxicity occurring within 30 days after coming off study was recorded.

Patients requiring a dose reduction of PEM and GEM were not re-escalated for the remainder of the study. When toxicity mandated a third dose reduction, the patient was withdrawn from the study. In the event of Grade 3 diarrhea, the subsequent dose of GEM and PEM was delayed until resolution of diarrhea and dosage was reduced by 25%. Grade 3/4 mucositis required a dose-reduction of 50%. For significant pleural or peritoneal effusions during therapy, drainage was indicated prior to the next treatment. Patients

were withdrawn from the study if the investigator believed the effusion represented progression of disease.

Statistical analysis

This study employed a two-stage multinomial phase II stopping rule design [17]. The addition of PEM to GEM was assumed to be inactive if the response rate was less than 20%, or the rate of early disease progression was more than 40%. The combination regimen was considered active if the response rate was more than 40% or the rate of early disease progression was less than 20%. In stage I, 15 patients were accrued and evaluated at 8 weeks post initiation of therapy. For the study to continue to stage II: (a) at least four patients had to have an objective tumor response with one or less patients with early disease progression; or (b) at least six patients had to have an objective tumor response with two or less patients with early disease progression; or (c) at least seven patients had to have an objective tumor response with three or less patients with early disease progression; or (d) at least eight patients with an objective tumor response regardless of the rate of early disease progression. If these criteria were not met, the study would not continue to the second stage of accrual. Survival curves were calculated using the Kaplan Meier method. Patients not experiencing an event were censored at the time of last follow-up.

Results

Patient characteristics

Between October 2004 and October 2005, 16 patients were enrolled. Patient characteristics are outlined in Table 1. The median age was 54 (range 33–77), 14 patients had a performance status of 0–1 and two patients had a performance status of 2. Twelve patients were post-menopausal, and the majority of patients were estrogen and progesterone receptors positive. HER-2 status was not done or unknown in most patients. Only two patients had not received any prior radiation treatment and 75% had received some hormonal therapy. Fourteen patients had received prior chemotherapy with six of these patients having received two prior regimens and three patients receiving three prior regimens.

Table 1 Patient characteristics

	No. of patients $n = 16$
Age (years, median (range)	54 (33–77)
Male:female	0:16
Menopausal status	
Pre-menopausal	1
Post-menopausal	12
Peri-menopausal	3
Performance status at baseline	
0	7
1	7
2	2
No. of disease sites	
<3 Sites	6
≥3 Sites	10
No. of prior chemotherapy regimens	
0	2
1	5
2	6
3	3
Prior therapy	
Surgery	16
Hormone therapy	12
Radiation therapy	14
Receptor status	
Estrogen receptor	
Positive	13
Negative	3
Progesterone receptor	
Positive	10
Negative	6
HER-2/neu assay	
Fish-and IHC 0, 1+, 2+	5
Fish N/D or unknown and IHC 0, 1+	9
Not done	2

Treatment delivery and toxicities

The median number of cycles received was 5 (range 1–13). Dose reductions were required for five patients and 12 cycles were delayed due to adverse events. Thirteen patients completed 4 cycles of therapy and three patients completed 12 cycles of therapy. Of the 16 patients entered, 3 completed the study, 6 discontinued due to progressive disease, 3 due to adverse events, 2 as per patient's decision, 1 due to lack of efficacy (patient/physician perception) and 1 did not meet the entry criteria (Table 2).

All patients were evaluable for toxicity. Toxicities are outlined in Table 3. There were no deaths during the treatment phase of the study. Five patients had at least one serious adverse event. Mild Grade 2 hematologic toxicity was reported in 11 patients. A total of three patients experienced febrile neutropenia. Three patients required blood products with one patient requiring transfusion of both red blood cells and platelets and one patient requiring red cell transfusions on two occasions. Treatment-related Grade 3/4 non-hematologic toxicity included one case each of: fatigue; skin rash; anorexia; elevation of liver transaminases;

Table 2 Patients disposition

No. of patients entered the study	16
Median number of cycles delivered	5 (range 1–13)
Primary reasons for discontinuation	
Lack of efficacy (progressive disease)	6
Completion of study	3
Adverse events	3
Patient's decision	2
Lack of efficacy (patient/physician perception)	1
Entry criteria not met	1

pulmonary infiltrates; pneumonia and arterial ischemia (Table 3). No patients died of drug-related toxicity.

Antitumor activity

Fourteen of the 16 patients were evaluable for efficacy analysis (Table 4). Disease was not re-evaluated in two patients. No responses (complete or partial) were observed in this study. Of the 14 evaluable patients, 7 patients had stable disease, 6 patients had progression of disease as the initial response evaluation and 1 evaluable patient had an objective response recorded as "unknown". Five patients died due to disease after coming off study.

In all treated patients ($n = 16$), median time to treatment failure was 1.9 months (95% CI: 1.4–4.0 months); median progression-free survival was 3.2 months (95% CI: 1.4–5.6 months) and median overall survival was 5.9 months (95% CI: 4.6–8.6 months). This study did not meet the criteria for proceeding to the second stage of accrual as the rate of early disease progression was more than 40% and the response rate was 0%.

Table 3 Treatment-related toxicities

Grade 3/4 toxicities	No. of patients (%)
Hematological toxicities	
Febrile neutropenia	3 (19)
Non-hematological toxicities:	
Fatigue	1 (6)
Skin rash	1 (6)
Anorexia	1 (6)
Lung infiltrate	1 (6)
Pneumonia	1 (6)
Elevation of liver transaminases	1 (6)
Arterial ischemia	1 (6)

Table 4 Clinical activity

No. of response-evaluable pts	14
Complete responses	0
Partial responses	0
Stable disease	7
Progressive disease	6
Unknown response	1

Discussion

In this phase II study, women with MBC who had received up to one prior regimen in the metastatic setting were treated with PEM following by GEM every 2 weeks for up to 12 treatments (12 cycles). Fourteen patients were evaluable for response and no objective responses were observed. A total of seven patients had stable disease, six patients had progressive disease and one patient had an "unknown" response (Table 4). These results are disappointing given the activity seen with GEM and PEM as single agents in this population and the activity seen when GEM has been combined with other chemotherapeutic agents.

The lack of activity seen with GEM and PEM in this study is in contrast to the 24% response rate (95% CI: 16–39%) noted by Ma et al. when both agents were administered every 21 days [13]. The different levels of activity seen in the two studies may be a reflection of different baseline characteristics of the patients entered, particularly with respect to the extent of prior therapy. The impact of the two-week schedule compared to a three-week schedule or the possibility that the results of one of these studies are spurious for reasons unknown can be entertained.

The median overall survival of 5.9 months experienced by women in this study is lower than the 10.3 months (95% CI: 8.3–18.9 months) that has been reported in the literature [13]. The majority of patients in this study had previously received one or more prior chemotherapy regimens, while only two patients were chemonaive. Three patients had received 3 prior chemotherapy regimens and all patients had received only one prior regimen for metastatic disease. We do not believe this population was more heavily pretreated than similar studies testing new therapies in MBC.

Though the overall dose of GEM and PEM administered was not markedly different from a conventional every 3-week schedule, it remains possible this schedule itself is suboptimal. While it is possible that higher doses of one or both of these agents would have resulted in greater activity, the reporting of Grade 3/4 hematological toxicities observed in this study suggests further dose escalation in this population would be ill-advised.

Another possibility is that the efficacy of the combination of these two agents is critically dependent on their schedule of administration and that a schedule in which GEM preceded PEM would have been more active. A recent

phase II randomized trial examining the schedule of administration of these two agents concluded that the most attractive regimen in a 21-day administration schedule was when PEM was administered prior to GEM [18].

Conclusion

PEM and GEM have shown activity as single agents in the treatment of MBC, however, the combination of PEM and GEM given in the dose and schedule utilized in this study was not efficacious. There are ongoing studies of this combination being completed and further development of this doublet in this schedule will be contingent upon the results of these trials.

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Conflict of interest statement None.

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