Phase I Trial of Intraperitoneal Pemetrexed, Cisplatin, and Paclitaxel in Optimally Debulked Ovarian Cancer


Abstract

Purpose: This phase I trial evaluated intraperitoneal (i.p.) pemetrexed, cisplatin, and paclitaxel in optimally debulked ovarian cancer.

Experimental Design: Dose escalation of day 1 i.p. pemetrexed accrued three patients to each of five dose levels (60–1,000 mg/m²), along with day 2 i.p. cisplatin (75 mg/m²) and day 8 i.p. paclitaxel (60 mg/m²). The goals were to determine maximum tolerated dose (MTD), 18-month progression-free survival (PFS), and pharmacokinetics of i.p. pemetrexed.

Results: Cycles, given every 21 days, had an 80% 6-cycle completion rate. There was minimal grade III to toxicitiy in the first 4 dose levels and remarkably an almost complete absence of peripheral neuropathy and alopecia. At the highest dose level, two of three patients experienced grade III and dose-limiting toxicity (DLT; hematologic, infection, gastrointestinal). There was a pharmacokinetic advantage for i.p. pemetrexed with an intraperitoneal:plasma area under the concentration–time curve ratio of 13-fold. Neither analysis of pharmacokinetic nor homocysteine levels explains the unexpected severity of toxicity in those two patients. On the basis of plasma C²₄h levels, the 42 cycles at 500 mg/m² i.p. pemetrexed without DLT, the MTD appears to be 500 mg/m². Median PFS is 30.1 months; 18-month PFS is 78.6% (median follow-up 22.4 months).

Conclusions: This i.p.-only regimen in front-line ovarian cancer is feasible with PFS in line with recent literature. We suggest phase II trials of this regimen in this population with i.p. pemetrexed at 500 mg/m². The favorable toxicity profile at doses <1,000 mg/m², which needs to be confirmed, appears to compare well with standard combination i.v./i.p. platinum/taxane chemotherapy in this disease.

Clin Cancer Res; 18(9); 2668–78. ©2012 AACR.

Introduction

Epithelial ovarian cancer continues to be the leading cause of gynecologic cancer death in the United States, with more than 21,990 new cases and 15,460 deaths expected in 2011 (1). Since the incorporation of taxanes into platinum-based therapy in the mid 1990’s, there has been little progress in achieving a further significant reduction in overall mortality. However, in optimally debulked stage III ovarian cancer, advances validated by several phase III trials and meta-analyses, include the introduction of i.p. therapy with cisplatin which has increased survival (2–7). Acute toxicity has been a significant barrier to universal acceptance of the i.p. approach (4, 5). Investigation into how to lengthen progression-free survivals (PFS) while lessening toxicity remains an area of active research.

Pemetrexed (Alimta) is a multitargeted antifolate, which has the ability to interfere with the synthesis of 3 folate-dependent enzymes (thymidylate synthase, dihydrofolate reductase, and glycaminamide ribonucleotide formyltransferase) involved in de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed, when given i.v., is broadly active in a wide variety of solid tumors, including mesothelioma, non–small cell lung cancer, and platinum-sensitive and -resistant ovarian cancer (8–15). Before the start of this trial, preliminary data from a GOG phase II trial using i.v. pemetrexed suggested that there was considerable activity in platinum-resistant ovarian cancer; these data were subsequently confirmed (12). A phase III trial showed that the addition of i.v. pemetrexed to i.v. cisplatin in patients with pleural mesothelioma significantly increased overall survival (OS) as well as PFS and reduced disease-related symptoms (8). In trials of pemetrexed in other solid tumors, treatment with folate and vitamin B₁₂ was shown to improve its toxicity profile and has significantly reduced grade III and IV toxicities.
Translational Relevance
We report the first front-line trial in patients with stage III optimally debulked ovarian cancer in which all drugs in combination (pemetrexed, cisplatin, paclitaxel) are given intraperitoneally. Moreover, this is the first report of intraperitoneal (i.p.) pemetrexed in ovarian cancer. We show a pharmacokinetic advantage to i.p. pemetrexed. At doses less than 1,000 mg/m² i.p. pemetrexed, the combination is very well tolerated with no more than grade 1 peripheral neuropathy or alopecia, and only 8.3% grade III hematologic toxicity. The median progression-free survival (PFS) of 30.1 months is consistent with other reports of combination i.v./i.p. chemotherapy in this disease. Our findings suggest pursuit of larger trials of this regimen at 500 mg/m² i.p. pemetrexed in combination with i.p. cisplatin and paclitaxel, which seems to have far less toxicity than standard i.v./i.p. cisplatin or carboplatin/taxane regimens.

Such as neutropenia and gastrointestinal toxicities, as well as mortality (8, 16). At the time of conception and initiation of this trial, there were no previously published reports on the use of i.p. pemetrexed in humans. Preclinical data in rats showed that administration of i.p. pemetrexed led to a significantly higher (up to 40.8-fold) i.p.i.v. area under the concentration–time curve (AUC, area under curve) ratio, than did an equivalent dose of i.v. pemetrexed (17). In addition, the knowledge that pemetrexed seeks out third spaces, such as the i.p. cavity, was felt to be an advantage that along with the higher AUC would increase the efficacy of this drug. Preclinical data showed that cisplatin does not affect the pharmacokinetics of pemetrexed (18); likewise those of total platinum are unaltered by pemetrexed administration (19). Therefore, the i.p. administration of pemetrexed and cisplatin was an appropriate choice.

In the design of this trial, the significant toxicity of the i.v. paclitaxel, i.p. cisplatin, and i.p. paclitaxel arm of the GOG-172 trial was taken into consideration (4). Because of the toxicity seen in the GOG trial many physicians were resistant to using i.p. chemotherapy, and off-trial modifications, including reduction of the i.p. cisplatin dose from 100 to 75 mg/m², were common. The AUC advantage of i.p. cisplatin in comparison with i.v. administration is at least 15; whereas remarkably the AUC advantage of i.p. paclitaxel is up to 1,000-fold higher than an equivalent dose administered i.v. (20). Given this context, the inclusion of i.v. paclitaxel may add neurologic toxicity without substantially adding to treatment efficacy. We reasoned that by replacing the i.v. paclitaxel with noncross-resistant i.p. pemetrexed, and giving the i.p. cisplatin at 75 mg/m², we would decrease the significant incidence and severity of neurotoxicity and other toxicities, while maintaining the efficacy.

Our phase I front-line trial in patients with optimally debulked stage III C ovarian, peritoneal, and tubal cancer, includes i.p. pemetrexed given day 1 along with i.p. cisplatin on day 2. Intraperitoneal paclitaxel is given on day 8 as in the highly active GOG-172 regimen. Our trial serves as the first trial in this disease to include i.p. pemetrexed. It is the first front-line trial in this disease in which all drugs in the combination are given intraperitoneally. The goal of the study was to determine the maximum tolerated dose (MTD) of this combination therapy and to determine its toxicity. Secondary goals were to determine the PFS with a goal of 80% of patients being progression-free at 18 months and to conduct correlative pharmacokinetic analysis of i.p. pemetrexed.

Materials and Methods
Patient eligibility
Patients who had a histologically or pathologically confirmed diagnosis of stage III carcinoma of the ovary, primary peritoneum, or fallopian tube were eligible if they (1) had no prior treatment and were optimally debulked at primary surgery to individual tumor plaques of less than 1 cm or (2) had received up to 4 cycles of i.v. carboplatin/taxane as neoadjuvant chemotherapy for advanced, unresectable disease and at interval surgery were optimally debulked to less than 1 cm.

Additional inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, adequate hepatic function [defined as serum bilirubin ≤2 times the upper limit of normal (ULN)] and alanine and aspartate transaminases ≤2.5 times the ULN], and adequate renal function, as defined by a creatinine clearance rate of ≥45 mL/min. Eligible patients were required to have a hemoglobin level of ≥9 g/dL, white blood cell count ≥3,500/µL, and platelets ≥100,000/µL. Patients with mild to moderate renal insufficiency (defined as a creatinine clearance between 45 and 79 mL/min) needed to be able to interrupt nonsteroidal antiinflammatory treatment for at least 2 days before, the day of, and at least 2 days after the administration of pemetrexed. Finally, patients must have been able to receive folic acid, vitamin B12, and dexamethasone treatments.

Exclusion criteria included life-threatening complications of their malignancies, severe, and/or uncontrolled concurrent medical disease (e.g., uncontrolled diabetes or heart disease, uncontrolled chronic renal or liver disease, or active uncontrolled infection). Additional exclusion criteria included presence of third space fluid not controllable by drainage, evidence of uncontrollable nausea, history of abdominal fistula, intraabdominal abscess or other contraindication to i.p. therapy, preexisting history of significant hearing loss, or known hypersensitivity to any component of pemetrexed, cisplatin, or paclitaxel. Eligible patients must not have a prior malignancy except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated stage I or II cancer from which the patient was in complete remission, or any other cancer from which the patient had been disease-free for 5 years.
All patients provided written informed consent before study enrollment. The study was approved by the University of Arizona (Tucson, AZ) Institutional Review Board (IRB) and was conducted in accordance with institutional and federal guidelines.

Study design and treatment
The study was an open label, escalating dose, phase I trial in patients with optimally debulked stage III ovarian, peritoneal, or fallopian tube cancer.

Intraperitoneal pemetrexed was administered on day 1, i.p. cisplatin dosed at 75 mg/m² on day 2, then i.p. paclitaxel dosed at 60 mg/m² on day 8 of each cycle with courses repeated every 21 days for 6 cycles. Rationale for sequencing pemetrexed day 1 and cisplatin day 2 comes from in vitro sequencing data suggesting that the preferred administration schedule to avoid antagonistic effects and to take advantage of their synergy, was to administer pemetrexed first followed by cisplatin (21). No dose reductions were required, and there were only 3 one-week dose delays. Patients were treated with i.p. pemetrexed at the following escalating dose levels: 60, 120, 500, 750, and 1,000 mg/m². If none of the initial 3 patients on a dose level experienced a dose-limiting toxicity (DLT) after the first cycle of therapy, then the dose was escalated to the next level. If 2 or more patients on any dose level experienced a DLT, then the MTD would be determined to be the next lower dose level. DLTs were defined as grade III or higher febrile neutropenia, thrombocytopenia with bleeding, neurologic toxicity, nonhematologic toxicities (not including fatigue, alopecia, nausea, vomiting, and elevated liver transaminases), and grade IV neutropenia lasting more than 7 days, thrombocytopenia, and increased liver transaminases. A total of 10 patients were to be treated at MTD.

Because there were no previously published reports in humans of i.p. pemetrexed, we started at a very low dose of 60 mg/m², knowing at the outset that the i.v. dose of pemetrexed given in combination was 500 mg/m² in other tumors (8, 9, 16). There were minimal grade III and no grade IV toxicities observed at dose levels ≤500 mg/m² i.p. pemetrexed. During the conduct of the trial more mature data on i.v. pemetrexed in ovarian cancer subsequently became available, with doses up to 900 mg/m² being active and tolerated (12). We therefore obtained IRB approval to continue the dose escalation up to 1,000 mg/m² i.p. pemetrexed. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Patients were given supplemental folic acid and vitamin B₁₂ to prevent the grade IV hematologic and grade III and IV nonhematologic toxicities associated with pemetrexed therapy. Folic acid (400–800 µg) was taken daily beginning at least 7 days before the first dose of pemetrexed and continuing until 3 weeks after the last dose of pemetrexed. Higher doses of folic acid have not been shown to be more effective in the prevention of pemetrexed toxicity (22). Vitamin B₁₂ (1,000 µg) was administered as an intramuscular injection 1 to 2 weeks before the first dose of pemetrexed and repeated every 9 weeks until 3 weeks after the last dose of pemetrexed. Strict attention was paid to patient adherence to folic acid and vitamin B₁₂. In addition, for rash prophylaxis, dexamethasone (4 mg oral or equivalent) was given twice daily the day before, the day of, and the day after pemetrexed administration.

Patient evaluation and definition of response
Before the beginning of each cycle, CA125, complete blood counts and serum chemistries were evaluated, creatinine clearance was calculated, and a physical examination was done. After the end of treatment, patients’ CA125 levels were measured and computed tomographic (CT) scans were carried out. Response to treatment was evaluated with posttreatment CT scans and measured changes in CA125 levels 6 months after the initiation of the treatment regimen, or within one month after discontinuation of treatment if stopped early. CA125 response in evaluable patients (N = 13) was analyzed using the modified Gynecologic Cancer Intergroup (GCIG) criteria (23). There was one evaluable patient by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. After completing the treatment, CA125 levels continued to be monitored and patients were seen for follow-up assessments of disease status. Consolidation treatment was given at the discretion of the individual provider after discussion with the patient.

Intraperitoneal port placement
All patients underwent i.p. port placement at the time of their primary laparotomy for ovarian cancer. The University of Arizona Cancer Center has several decades of experience in i.p. chemotherapy and the gynecologic oncologists who did the surgeries have extensive experience in i.p. chemotherapy. Single-lumen implantable ports (Bard Access Systems, Inc.) were placed with permanent sutures anchoring the port in place. There were no dose delays or discontinuation of i.p. chemotherapy due to i.p. catheter complications. Only one i.p. catheter revision was necessary which occurred before start of the i.p. treatment regimen.

Statistical analysis
PFS was defined as the time from the start of therapy to the time of first documentation of progression or death due to any cause; PFS and OS were estimated using the Kaplan–Meier method. Statistical analysis was carried out with the SAS statistical package, version 9.2.

Pemetrexed assay
Intraperitoneal fluid samples were obtained when possible from the i.p. port for analysis. Cycle 1 was intended to be the cycle for pharmacokinetic sample draws, but later cycle draws were also used for these analyses due to the difficulty of obtaining i.p. fluid. Fortunately, the pharmacokinetics of pemetrexed have been observed to remain stable/consistent over multiple treatment cycles (package insert for Alimta, Pharmacokinetics section).

Plasma and i.p. fluid pemetrexed concentrations were analyzed by a published liquid chromatography/tandem mass spectrometry (LC/MS-MS) method (24) with minor...
modifications. Briefly, diluted plasma or i.p. fluid samples (0.1 mL) were mixed with the internal standard solution (0.02 mL of 1 μg/mL of methotrexate in saline) and ice-cold methanol (0.2 mL). An aliquot of the supernatant was injected onto the LC/MS-MS system. The LC/MS-MS system consisted of a Surveyor HPLC system and a TSQ Quantum Ultra triple quadrupole mass spectrometer (Thermo Electron). Chromatographic separation of pemetrexed and the internal standard was achieved on an Xterra MS C-18 column (3.9 × 50 mm, 3.5 μm; Waters) with a gradient mobile phase consisting of 10 mmol/L formic acid and acetonitrile. The mass spectrometric analysis was done with the electrospray ionization interface operated in the positive polarity mode. The selected reaction monitoring transition was: 428.1 → 281.1 for pemetrexed and 455.2 → 308.1 for the internal standard. Calibration curves were prepared either in plasma diluted with PBS at the same dilution as the plasma samples or in PBS for the i.p. fluid samples. Linear calibration range was established for the pemetrexed concentrations of 1 to 1,500 ng/mL.

Homocysteine levels

Homocysteine levels (chemiluminescent immunoassay; Abbott Laboratories) were measured in the plasma samples before, and at 24 hours after i.p. pemetrexed administration for cycle 1, as a marker of functional folate status. Baseline homocysteine levels have been shown to correlate with severe toxicity from pemetrexed in pooled trials (25).

Results

Patients

Fifteen patients were enrolled and treated on this study, with 3 patients on each of the 5 dose levels. Baseline characteristics are shown in Table 1. All patients had stage IIIC ovarian, peritoneal, or tubal cancer. Three of 15 patients had bulky disease and received neoadjuvant chemotherapy consisting of i.v. carboplatin and paclitaxel for 3 or 4 cycles before their debulking surgery. All 15 patients were optimally debulked to less than 1 cm residual disease, with one third of patients undergoing small or large bowel resections as part of the debulking procedure. There was a median of 23 days (range, 9–41) from surgery to the start of treatment. A total of 80 cycles of pemetrexed were administered, with 12 of 15 patients (80%) completing all 6 cycles of i.p. chemotherapy. One patient was in cycle 5 at dose level 2 (120 mg/m2) when she experienced a seizure of grade III toxici-

Table 1. Patient and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>65 (46–76)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>0 7 (46.7) 1 8 (53.3)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td>White, Hispanic 3 (20.0) White, non-Hispanic 12 (80.0)</td>
</tr>
<tr>
<td>Primary site, n (%)</td>
<td>Ovarian 10 (66.7) Fallopian tube 3 (20.0) Peritoneal 2 (13.3)</td>
</tr>
<tr>
<td>FIGO stage, n (%)</td>
<td>IIIC 15 (100.0)</td>
</tr>
<tr>
<td>Cell type, n (%)</td>
<td>Serous 13 (86.7)  Mixed epithelial 1 (6.7) Other 1 (6.7)</td>
</tr>
<tr>
<td>Tumor grade, n (%)</td>
<td>2 1 (6.7) 3 14 (93.3)</td>
</tr>
<tr>
<td>Primary site, n (%)</td>
<td>Ovarian 10 (66.7) Fallopian tube 3 (20.0) Peritoneal 2 (13.3)</td>
</tr>
<tr>
<td>Residual disease, n (%)</td>
<td>5 (33.3) &lt;1 cm 10 (66.7)</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy, n (%)</td>
<td>Yes 3 (20.0) No 12 (80.0)</td>
</tr>
</tbody>
</table>


response by RECIST, received further treatment with i.v. carboplatin, paclitaxel, and bevacizumab.

Toxicity

There was little grade III and no grade IV toxicities observed in the first 4 dose levels (Table 2). The most common grade III toxicity was fatigue (25%). The most common grade I or II toxicity was gastrointestinal (grade II nausea, 41.7%). Remarkable was the almost complete absence of neuropathy or alopecia, given that 100% of these subjects had completed 5 cycles, and 91%, 6 cycles.

Table 3 represents the toxicities of the 3 patients observed at dose level 5 (1,000 mg/m2 i.p. pemetrexed). Hundred percent of the ≥ grade III toxicities observed were experienced by 2 of the patients (subjects 014 and 015). Their toxicities are those commonly attributed to pemetrexed and include hematologic, infection, gastrointestinal toxicity, fatigue, and metabolic toxicities. In the 2 patients who experienced increased toxicity, we confirmed with the
patient and family that they had been compliant with folic acid (the timing of the vitamin B₁₂ injections having been confirmed to be in compliance). Subject 015, after receiving day 1 (i.p. pemetrexed) of cycle 1, succumbed to the consequences of her opportunistic infection in the setting of grade IV neutropenia, thrombocytopenia, and grade III diarrhea, and oral mucositis. Subject 014, having received cycle 2, survived her infection in the setting of her grade IV neutropenia, thrombocytopenia, anemia, and grade III diarrhea. Upon recovery from the acute event and without any further therapy, she remained NED 406 days from start of the i.p. pemetrexed regimen. The remaining patient (subject 012) treated at this dose level suffered only grade I or II toxicities similar to that seen at the lower dose levels.

Because at 1,000 mg/m² i.p. pemetrexed, 2 of 3 patients incurred DLTs, the MTD of this regimen may be 750 mg/m². However, in light of the unexpected severity of these toxicities in 2 patients at this dose level, the trial was put on hold to allow pharmacokinetic analyses in an attempt to better understand the reasons for these events, and to help determine what lower dose level may be safe. No additional patients were accrued on this study.

**Efficacy**
Fourteen patients were evaluable for efficacy measurements. The majority of patients were evaluable by CA125 (N = 13), only one patient by RECIST, as all patients had been optimally debulked at surgery. Twelve patients were NED by CT scan at the end of the regimen. One additional patient was evaluable by RECIST and met criteria for a partial response. The remaining patient (subject 014) had ascites only on her CT scan which proved to be nonmalignant. Interestingly, following the acute toxicities, she was plagued with recurrent exudative nonmalignant ascites, confirmed by serial paracentesis, for several months after discontinuation of the regimen. Out of 13 evaluable patients by CA125, there was 100% response, with 12 complete responses (CR) and 1 partial response. Five of 14 patients have recurred, with 2 deaths.

With a median follow-up time of 22.4 months, the median PFS was 30.1 months and the median OS has not
been reached (Fig. 1). The 6-month PFS was 100%; 12-month PFS, 85.7%; and 18-month PFS, 78.6%. Thus, our secondary goal of PFS at 18 months of 80% was almost reached.

**Pharmacokinetic analysis**

Figure 2A illustrates the average plasma concentration–time profile of pemetrexed after i.p. administration of 500, 750, and 1,000 mg/m². Between 0.5 to 4 hours after initiation of i.p. administration, the plasma concentrations in most patients were maintained at relatively constant levels. Plasma concentrations declined significantly 24 hours after initiation of i.p. administration. Figure 2B illustrates the plasma and i.p. fluid concentration–time profile of 2 patients after i.p. administration of 1,000 mg/m². The i.p. concentrations were consistently higher than the plasma concentrations in both patients. Similarly, the i.p. concentrations declined significantly 24 hours after initiation of i.p. administration.

Table 4 summarizes the pharmacokinetic parameters of pemetrexed after i.p. administration of 500, 750, and 1,000 mg/m². The average plasma \( C_{\text{max}} \) showed a less than proportional increase as the dose was increased to 1,000 mg/m² (25.1 ± 1.3, 39.3 ± 7.3, and 38.7 ± 11.2 μg/mL for 500, 750, and 1,000 mg/m², respectively). The average plasma \( \text{AUC}_{0-24h} \) increased proportionally as the dose was increased to 1,000 mg/m² (293.5 ± 42.0, 422.2 ± 57.9, 566.8 ± 182.1 μg/mL × h for 500, 750, and 1,000 mg/m², respectively). The plasma pemetrexed concentration at 24 hours after initiation of dosing exhibited a more than proportional increase as the dose was increased to 1,000 mg/m² (0.674 ± 0.998, 0.418 ± 0.054, and 13.8 ± 16.6 μg/mL for 500, 750, and 1,000 mg/m² dose levels, respectively). Intraperitoneal fluid samples were not able to

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
<th>Grade V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fatigue</td>
<td>0 (0)</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Alopecia</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other—skin</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Anorexia</td>
<td>0 (0)</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Nonmalignant ascites</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (66.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Oral mucositis</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Rectal bleeding</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Infection</td>
<td>Febrile neutropenia</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Infection—abdomen</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Opportunistic infection</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Creatinine</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Hypomagnesemia</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Weakness</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
be collected for patients receiving 500 and 750 mg/m² doses and were collected at only 2 time points for patient 014 receiving 1,000 mg/m². Serial i.p. fluid samples were available from the remaining 2 patients receiving the 1,000 mg/m² dose. The i.p. fluid to plasma pemetrexed $C_{\text{max}}$ ratio for these 2 patients was 13.9 and 7.9, and the AUC$_{0–24h}$ ratio was 13.0 and 4.0.

These data show a pharmacokinetic advantage (by $C_{\text{max}}$ of up to 14-fold, and by AUC of up to 13-fold) for i.p. pemetrexed at the 1,000 mg/m² dose level. While there was a proportional increase in plasma AUC with increasing dose level, reflecting linear kinetics for AUC, what is striking is that at the 1,000 mg/m² dose, the 24 hours plasma pemetrexed concentration was still quite elevated, more than 20-fold higher and out of line with that observed at the lower doses.

This analysis however did not explain why 2 patients (subjects 014 and 015) at the 1,000 mg/m² dose level experienced excess toxicity whereas subject 012 at the same dose level did not. Figure 2B shows paradoxically, that the pemetrexed plasma concentrations in subject 012 (top curve) were significantly higher than for subject 015 (bottom curve). Similarly Table 4 shows that the i.p. $C_{\text{max}}$ and AUC for subject 012 were higher than for subject 015, and the plasma AUC and $C_{24h}$ were higher than for subject 014. Subject 015, who died from toxicity, had the highest plasma $C_{24h}$ level of the whole study.

In a further attempt to find a basis for the increased toxicity in subjects 014 and 015, we next investigated plasma homocysteine levels, as levels more than 11.5 $\mu$mol/L were associated with a high risk for severe toxicity from pemetrexed (25). Homocysteine can serve as a marker of functional folate status. At dose levels less than 1,000 mg/m², homocysteine levels were normal both pre- and 24 hours post-intraperitoneal pemetrexed administration. At the 1,000 mg/m² dose subjects 012 and 015, but not subject 014, had high levels above this cutoff both pre-intraperitoneal pemetrexed and at the 24 hours time point.
In subject 015, the pemetrexed treatment increased the homocysteine level further (e.g., lowered the functional folate level) when compared with the pretreatment level. This may be secondary to the high plasma pemetrexed levels detected at this time point. This also suggests that her functional folate status was inadequate, and that she was at risk for excess toxicity. This finding was not observed for subject 014 who also experienced excess toxicity, but who appeared to have an adequate folate status at least for the first cycle when these samples were drawn.

Taken together, analyses of our pharmacokinetic and homocysteine levels do not clearly explain the excess toxicities observed in 2 of 3 patients at the highest dose level. The elevated plasma $C_{24h}$ levels do stand out, however, for this dose level. In contrast, at both the 500 and 750 mg/m$^2$ dose levels, the plasma $C_{24h}$ levels were low at less than 1 $\mu$g/mL (Table 4). A total of 7 patients received i.p. pemetrexed for 6 cycles each (total 42 cycles), at dose levels $\geq$500 mg/m$^2$, without excessive toxicity. Our available data therefore can support a MTD at 500 mg/m$^2$ i.p. pemetrexed, although we cannot rule out a MTD as high as 750 mg/m$^2$.

### Discussion

Our trial represents the first regimen for patients with front-line advanced stage optimally debulked ovarian (including peritoneal and tubal) cancer in which all the drugs in the combination are given intraperitoneally. We show that this i.p.-only approach is feasible front-line, as our median PFS of 30.1 months is in line with the literature of patients with stage III ovarian cancer who receive front-line i.v./i.p. cisplatin or carboplatin/taxane chemotherapy (3, 4, 26–33). While the doses and drugs vary from study to study, and some of the studies include i.v. neoadjuvant chemotherapy as do ours, the median PFS in these studies ranges from 19 to 29 months. Our 6-cycle completion rate of 80% is similar to the 71% for GOG-114 and significantly better than the 42% for GOG-172 (3, 4). Intraperitoneal catheter complications in our study were minimal and did not result in any dose delays or discontinuations of treatment. While direct comparisons cannot be made and our results confounded in part by the use of consolidation therapy in some patients, our PFS rate at 6, 12, and 18 months were at least as good as for GOG-172 (4). At 18 months, our PFS rate was 78.6% compared with approximately 60% for GOG-172.

This is also the first report of i.p. pemetrexed administration in ovarian cancer. For dose levels less than 1,000 mg/m$^2$ i.p. pemetrexed, the relative lack of toxicity compared with i.v./i.p. cisplatin or carboplatin/taxane chemotherapy was very apparent. There was minimal if any alopecia or neuropathy and almost no grade III or IV hematologic toxicity from the replacement of i.v. paclitaxel with i.p. pemetrexed. Among grade III or IV toxicities, only fatigue results confounded in part by the use of consolidation therapy in some patients, our PFS rate at 6, 12, and 18 months were at least as good as for GOG-172 (4). At 18 months, our PFS rate was 78.6% compared with approximately 60% for GOG-172.

Intraperitoneal Pemetrexed, Cisplatin, and Paclitaxel in Ovarian Cancer

### Table 4. Pharmacokinetic parameters after i.p. administration of pemetrexed

<table>
<thead>
<tr>
<th>Dose, mg/m$^2$</th>
<th>$C_{\text{max}}$, $\mu$g/mL</th>
<th>AUC$_{0-24h}$, $\mu$g/mL $\times$ h</th>
<th>$C_{24h}$, $\mu$g/mL</th>
<th>$C_{\text{max}}$, $\mu$g/mL</th>
<th>AUC$_{0-24h}$, $\mu$g/mL $\times$ h</th>
<th>$C_{24h}$, $\mu$g/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 Subject 006</td>
<td>25.6</td>
<td>301.0</td>
<td>0.119</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Subject 007</td>
<td>26.5</td>
<td>248.2</td>
<td>0.076</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Subject 008</td>
<td>24.0</td>
<td>331.2</td>
<td>1.826</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Mean $\pm$ SD</td>
<td>25.1 $\pm$ 1.3</td>
<td>293.5 $\pm$ 42.0</td>
<td>0.674 $\pm$ 0.998</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>750 Subject 009</td>
<td>46.8</td>
<td>452.6</td>
<td>0.451</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Subject 010</td>
<td>47.0</td>
<td>482.8</td>
<td>0.448</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Subject 011</td>
<td>34.3</td>
<td>370.9</td>
<td>0.356</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Mean $\pm$ SD</td>
<td>39.3 $\pm$ 7.3</td>
<td>422.2 $\pm$ 57.9</td>
<td>0.418 $\pm$ 0.054</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1,000 Subject 012</td>
<td>51.6</td>
<td>722.8</td>
<td>5.42</td>
<td>719.4</td>
<td>9,394.1</td>
<td>22.6</td>
</tr>
<tr>
<td>Subject 014</td>
<td>31.6</td>
<td>366.6</td>
<td>3.07</td>
<td>ND</td>
<td>ND</td>
<td>22.3</td>
</tr>
<tr>
<td>Subject 015</td>
<td>33.0</td>
<td>611.1</td>
<td>33.0</td>
<td>260.3</td>
<td>2,430.3</td>
<td>32.7</td>
</tr>
<tr>
<td>Mean $\pm$ SD</td>
<td>38.7 $\pm$ 11.2</td>
<td>566.8 $\pm$ 182.1</td>
<td>13.8 $\pm$ 16.6</td>
<td>489.8 $\pm$ 324.7</td>
<td>5,912.2 $\pm$ 4,924.1</td>
<td>25.9 $\pm$ 5.96</td>
</tr>
</tbody>
</table>
possible that our gastrointestinal and infection toxicities may be higher at this dose of i.p. pemetrexed than in the i.v./i.p. literature. Certainly the patient mortality and other near mortality in this small trial are notable.

The severe toxicities in the 2 patients at the highest dose level remain largely unexplained by pharmacokinetic analyses or homocysteine levels. The toxicities observed were identical to those seen in patients not supplemented with folate or vitamin B12. Folate/vitamin B12 supplementation does not completely protect from pemetrexed toxicity, however (16). Also, these toxicities did not appear to be ameliorated by leucovorin infusion in the one patient who was able to receive the rescue drug. The one pharmacokinetic finding which stood out was the more than 20-fold significantly elevated plasma pemetrexed concentrations 24 hours after i.p. drug delivery at this dose level, not seen at lower dose levels. In retrospect, although there were no DLTs, had we terminated the study early at 500 or 750 mg/m² i.p. pemetrexed, we would likely have avoided the excess toxicity we observed. A limitation of this study is that the MTD was not definitively determined, in that the trial did not proceed to accrue additional patients at a dose level less than 1,000 mg/m². On the basis of the C_{24h} pemetrexed levels, the number of patients in this study who tolerated ≥500 mg/m² without DLT, and in the context of the pharmacokinetic advantage of i.p. pemetrexed, we have evidence to suggest that the 500 mg/m² i.p. pemetrexed dose could serve as the MTD of this regimen.

After we opened this trial, several reports appeared of i.v. pemetrexed, single agent and in combination, in ovarian cancer (10–15). In patients with platinum-sensitive recurrent ovarian cancer and in combination with carboplatin, i.v. pemetrexed doses up to 900 mg/m² were well tolerated and active (10, 11). In one of these studies the response rate was 84% (11). In patients with platinum-resistant ovarian cancer, i.v. single-agent pemetrexed was tolerable up to 900 mg/m² with response rates up to 21% and stabilization rates up to 35% (12). There was however, more significant toxicity with 900 mg/m² i.v. pemetrexed than at the 500 mg/m² dose (13). Thus at this time, there is even a greater rationale for the pursuit of study of this regimen with i.p. pemetrexed at 500 mg/m² in patients with front-line platinum-sensitive ovarian cancer, especially given the extremely low toxicity profile at this dose.

In support of the i.p. pemetrexed approach, is a phase II study of i.p. pemetrexed at 500 mg/m² and i.p. cisplatin at 75 mg/m² in patients with diffuse malignant peritoneal mesothelioma, presented in 2010 (34). These patients had been optimally debulked and treated intraoperatively with hyperthermic chemotherapy. In this phase II trial, 90% of patients completed all 6 cycles and there were no grade III or IV toxicities. At this i.p. pemetrexed dose, preliminary pharmacokinetic analysis suggests a peritoneal fluid to plasma AUC ratio of 70, which is higher than what we obtained at 1,000 mg/m² i.p. dose of pemetrexed. We were unfortunately unable to measure i.p. AUC at the 500 mg/m² dose level. In rats given i.p. pemetrexed, the peritoneal fluid to plasma AUC ratio of 19.2 to 40.8 (17) is intermediate to our results and those obtained in the mesothelioma study (34). Plasma concentrations in the mesothelioma study were approximately half of ours at the same dose level but similar to our data, the plasma levels were sustained 4 hours after i.p. administration of pemetrexed (34). In studies of patients with mucinous peritoneal carcinomatosis, several factors were studied which were found not to significantly affect pharmacokinetics of hyperthermic i.p. chemotherapy (35, 36). What is unknown is whether i.p. pemetrexed pharmacokinetics is altered in the setting of prior hyperthermic i.p. chemotherapy-treated mesothelioma as compared with i.p. chemotherapy naive ovarian cancer. Regardless, the finding of such a large pharmacokinetic advantage for i.p. pemetrexed at 500 mg/m², and the significant lack of toxicity, is encouraging.

In summary, the pharmacokinetic advantage of i.p. pemetrexed favors pursuit of this route for administration of pemetrexed in ovarian cancer. It is clear that this drug has considerable activity in this disease. The 500 mg/m² dose of i.p. pemetrexed in combination with standard doses of i.p. cisplatin and i.p. paclitaxel seems to have a favorable toxicity profile, which needs to be confirmed by larger studies, compared to i.v./i.p. cisplatin or carboplatin/taxane therapy. Our experience with this regimen strongly suggests that it is the i.v. paclitaxel which significantly contributes to grade III or IV toxicities of i.v./i.p. therapy, rather than the i.p. cisplatin (at a dose of 75 mg/m²) or i.p. paclitaxel.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: S.K. Chambers, M.C. Clouser, D.S. Alberts
Development of methodology: S.K. Chambers, M.C. Clouser, D.S. Alberts
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.K. Chambers, H.-H.S. Chow, M.F. Janieck, J.M. Cragun, K.D. Hatch, J.L. Cohen, H.M. Wright
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.K. Chambers, H.-H.S. Chow, H. Cui, D.S. Alberts
Writing, review, and/or revision of the manuscript (i.e., statistical analysis, data interpretation,Drafting the manuscript, editing): S.K. Chambers, H.-H.S. Chow, J.M. Cragun, G. Cui, C. Laughren, M.C. Clouser, A. Shahin, D.S. Alberts
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Laughren, J.L. Cohen, H.M. Wright, D.S. Alberts
Study supervision: S.K. Chambers, M.C. Clouser

Acknowledgments

The authors thank Paul H. Sugarbaker, MD, for his advice and insight.

Grant Support

This work was supported in part by the NIH Cancer Center support grant CA-023074, including contributions from the Clinical Research, Biometry, and the Analytical Chemistry Shared Services and Women’s Cancers of the University of Arizona Cancer Center, Tucson, AZ; and by an Investigator Initiated Grant from Lilly Oncology, El Lilly Co., Indianapolis, IN.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received January 26, 2012; accepted February 15, 2012; published OnlineFirst March 15, 2012.

References


Phase I Trial of Intraperitoneal Pemetrexed, Cisplatin, and Paclitaxel in Optimally Debulked Ovarian Cancer


Updated version  Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-12-0261

Cited articles  This article cites 32 articles, 12 of which you can access for free at: http://clincancerres.aacrjournals.org/content/18/9/2668.full#ref-list-1

Citing articles  This article has been cited by 1 HighWire-hosted articles. Access the articles at: http://clincancerres.aacrjournals.org/content/18/9/2668.full#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.