Phase I and pharmacokinetic study of the multitargeted antifolate pemetrexed in combination with oxaliplatin in patients with advanced solid tumors

J. L. Misset1*, E. Gamelin2, M. Campone3, S. Delaloge4, J. E. Latz5, L. Bozec6 & P. Fumoleau3

1Hôpital Saint Louis, Paris; 2Centre Paul Papin, Angers; 3Centre René Gauducheau Nantes, St Herblain; 4Institut Gustave Roussy (IGR), Villejuif, France; 5Eli Lilly and Company, Indianapolis, IN, USA; Eli Lilly and Company, Suresnes, France

Received 5 November 2003; revised 16 March 2004; accepted 17 March 2004

Background: This phase I and pharmacokinetic study of pemetrexed in combination with oxaliplatin was performed to determine the maximum tolerated dose (MTD), and to evaluate safety and pharmacokinetics in patients with metastatic solid tumors.

Patients and methods: Pemetrexed was administered as a 10-min i.v. infusion followed 30 min later by oxaliplatin as a 2-h infusion, once every 21 days. Up to two previous chemotherapy regimens were allowed. Vitamin B12 supplementation and folic acid were not included in this study.

Results: Thirty-six patients were treated in six escalating dose levels. Dose-limiting toxicities at dose level 6 (pemetrexed 500 mg/m2 plus oxaliplatin 130 mg/m2) were febrile neutropenia, grade 3–4 diarrhea and grade 3 paresthesia. The MTD was not reached. The most common toxicity was neutropenia, with grade 3–4 occurring in 61% of patients. The pharmacokinetics of this pemetrexed–oxaliplatin combination are consistent with those following single-agent administration. Five responses (all partial) were observed over a broad range of solid tumors.

Conclusions: This pemetrexed–oxaliplatin combination (without vitamin supplementation) every 21 days can be administered using full therapeutic doses of each agent with acceptable tolerability and no overlapping toxicity. The recommended regimen for phase II studies is pemetrexed 500 mg/m2 plus oxaliplatin 120 mg/m2.

Key words: oxaliplatin, pemetrexed, pharmacokinetic, phase I study

Introduction

Pemetrexed is a novel, multi-targeted antifolate that inhibits several folate-dependent enzymes involved in the de novo pathways of pyrimidine and purine biosynthesis [1]. Its primary mechanism of action is the inhibition of thymidylate synthase, which results in decreased thymidine being necessary for DNA synthesis [2–6]. Pemetrexed is also a potent inhibitor of dihydrofolate reductase and glycaminide ribonucleotide formyl transferase, enzymes involved in purine synthesis. Pemetrexed has demonstrated broad antitumor activity in a variety of in vitro tumor cell lines, and is active against lymphoma, colon, lung, pancreas and breast cancer xenografts in vivo [7, 8]. On the basis of previous clinical phase I studies, a schedule of 600 mg/m2 pemetrexed given as a 10-min infusion once every 21 days was the recommended regimen for further development of single-agent pemetrexed [9, 10]. Phase II studies have yielded response rates ranging from 6% to 31% in a wide variety of tumors [11]. Toxicity seen in the phase II program led to the reduction of the dose to 500 mg/m2.

Oxaliplatin is a diamino-cyclohexane-containing platinum compound that inhibits DNA replication and transcription by forming DNA adducts. Its mechanism of action is similar to that of the classic platinum drugs, but molecular pharmacology studies suggest that oxaliplatin represents a distinct family of platinum compounds [12]. Preclinical evidence suggests that oxaliplatin is not cross-resistant with cisplatin or carboplatin [13–15]. Moreover, oxaliplatin has shown activity in cisplatin-resistant cell lines [16] and appears to interact synergistically with pemetrexed [17] and 5-fluourouracil (5-FU) [18, 19], as well as with gemcitabine [20] and irinotecan [21].

The clinical activity of oxaliplatin monotherapy has been best characterized in metastatic colorectal and ovarian cancers [22–27]. Oxaliplatin has demonstrated substantially less nephrotoxicity, ototoxicity and myelosuppression than cisplatin, and can be administered safely without specific hydration in an outpatient setting. Phase II studies have yielded overall response rates of ~20% in patients with untreated colorectal cancer [22–24], 10% in colorectal cancer patients resistant to
5-FU [24–26], and 30% in previously treated ovarian cancer patients [27].

On the basis of the broad activity of pemetrexed and oxaliplatin as single agents in human solid tumors, their different mechanisms of action and potential synergistic interaction, we decided to explore the combination of pemetrexed and oxaliplatin in a phase I clinical trial in patients with metastatic solid tumors. The principal objectives were to determine: (i) the maximum tolerated dose (MTD) of pemetrexed and oxaliplatin; (ii) the DLTs of the combination; (iii) the recommended dose of the combination for subsequent phase II trials; and (iv) the pharmacokinetic characteristics of the combination regimen.

Patients and methods

Patient selection

Patients with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic malignant solid tumor not amenable to curative therapy were eligible. Other eligibility criteria included age ≥ 18 years, World Health Organization (WHO) performance status ≤ 2, an estimated life expectancy of at least 12 weeks, and adequate bone marrow [platelets ≥ 100 x 10^9/L, hemoglobin ≥ 9 g/dL, absolute granulocyte count (AGC) ≥ 2 x 10^9/L], hepatic [bilirubin ≤ 1.5 x upper limit of normal, aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3 x normal (AST and ALT ≤ 5 x normal is acceptable if due to liver metastases), and albumin ≥ 2.5 g/dL] and renal function (calculated creatinine clearance ≥ 45 mL/min). Up to two previous chemotherapy regimens were allowed, but not within 4 weeks of enrollment (6 weeks for nitrosoureas or mitomycin). Previous radiotherapy was allowed if patients were treated at least 12 months previously. Patients were excluded from the study for: plasma homocysteine > 12 μmol/l; active infection; symptomatic brain metastasis; previous treatment with pemetrexed or previous oxaliplatin within 6 months of enrollment; previous high-dose chemotherapy with autologous stem-cell rescue; evidence of peripheral neuropathy grade > 1 according to the National Cancer Institute common toxicity criteria (NCI-CTC); inability to discontinue administration of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) 2 days before (5 days for long half-life NSAIDs) the day of, and 2 days after, therapy; or clinically significant effusions (pleural or peritoneal).

The study was conducted according to Good Clinical Practices and was approved by the local ethics committee. All patients gave written informed consent.

Treatment

Patients were administered pemetrexed (ALIMTA®; Eli Lilly and Co., Indianapolis, IN, USA) as a 10-min i.v. infusion at a starting dose of 300 mg/m², and oxaliplatin (ELOXATIN®; Sanofi-Synthelabo, Paris, France) as a 2 h i.v. infusion (without specific hydration) at a starting dose of 85 mg/m², exactly 30 min after the end of the pemetrexed infusion. Both drugs were given on day 1 every 21 days. Patients continued study treatment until disease progression, unacceptable toxicity or patient refusal.

Before the start of any cycle, absolute granulocyte count (AGC) had to be ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L. Treatment could be delayed up to 3 weeks to allow sufficient recovery, after which time patients may have been retreated at reduced doses depending on hematologic values. In case of grade 3 or 4 non-hematologic toxicity, pemetrexed was withheld until resolution, then restarted at a 25% dose reduction. Pemetrexed was given at 75% and 50% of the previous dose for grade 3 and 4 mucositis, respectively. If grade 3 or 4 neutropenia or mucositis recurred after two dose reductions, the patient was discontinued from the study. A patient who could not be administered drugs for 42 days from the time of last treatment was to be discontinued from the study. Neurotoxicity was graded using an alternative toxicity scale, modified by Levi et al., that considered the duration of neurological symptoms [28].

Concomitant treatments included antiemetics and oral dexamethasone 4 mg or equivalent, twice a day on the day before, the day of, and the day after pemetrexed administration. Granulocyte-colony stimulating factors (G-CSF) could be used only for patients with AGC < 0.5 x 10^9/L for at least 5 days, neutropenic fever, or documented infection while neutropenic. Leucovorin rescue was allowed for grade 4 myelosuppression lasting ≥ 5 days, and for grade 3 or 4 mucositis. Vitamin B12 supplementation and folic acid were not included in the study regimen, because at the time of enrollment the decision had not yet been made to supplement all patients; however, patients with plasma homocysteine ≥ 12 μmol/l were excluded from the study.

Dose escalation

Six dose levels of pemetrexed and oxaliplatin were tested at a starting dose level of pemetrexed 300 mg/m² plus oxaliplatin 85 mg/m². At least three consecutive patients were treated at each dose level. If none of the three patients had DLT during the first cycle, patients in the next dose level were treated. If one of three patients had DLT, three additional patients were included at that dose level. If at least two patients had DLT, then dose escalation was stopped and that dose level was established as the MTD. An additional three or six patients were treated at the previous dose level, for a total of nine patients treated. If at this dose level, DLT did not occur in three or more of nine patients, this dose level was considered the recommended dose for phase II studies. If the study advanced to the highest dose level (dose level 6: pemetrexed 500 mg/m² plus oxaliplatin 130 mg/m²) and more than two patients developed DLT, additional patients were treated until a total of 16 patients were treated or until a total of six patients had DLT, whichever came first. If two of the first six patients or (if additional patients were treated) a total of six patients had DLT, the previous dose level was considered the recommended phase II regimen; if more than six of the 16 patients had DLT, dose level 6 was considered the recommended dose for phase II studies.

The DLT was defined as the occurrence of one of the following events during the first cycle: NCI-CTC grade 4 neutropenia persistent for ≥ 7 days, febrile neutropenia (defined as grade 4 neutropenia with fever > 38.5°C and/or concomitant systemic infection), grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding requiring platelet transfusions, grade ≥ 3 non-hematologic toxicity (excluding alopecia, nausea/vomiting), elevated aspartate aminotransferase and alanine aminotransferase levels three or more times the baseline value, or persistence of grade ≥ 2 non-hematologic toxicity (excluding alopecia).

Baseline and treatment

Before entry into the study, patients underwent complete medical history and clinical examination including vital signs, concomitant treatments, performance status, hematologic and biochemical profiles, plasma homocysteine, electrocardiogram and chest X-ray, and tumor target assessments. Patients who received at least one dose of either pemetrexed or oxaliplatin were evaluated for toxicity. Toxicity was graded before each cycle according to NCI-CTC. Clinical examinations were performed every cycle. Hematologic profiles were performed before each cycle and weekly. Non-hematologic laboratory profiles were performed before each cycle.
Pharmacokinetic sampling was performed on all enrolled patients. Blood samples were drawn during the first treatment cycle for the determination of pemetrexed and total platinum in plasma. Samples were drawn from the arm contralateral to the infusion line. Heparinized plasma samples were analyzed for pemetrexed using validated LC-ESI-MS-MS (liquid chromatography with electrospray ionization and tandem mass spectroscopy detection) methods over the concentration ranges of 10–2000 ng/ml and 1000–200,000 ng/ml, by Taylor Technology, Inc. (Princeton, NJ, USA). Heparinized plasma samples were analyzed for total platinum derived from oxaliplatin using a validated inductively coupled plasma mass spectrometry method over the concentration range 3–4000 ng/ml by Laboratoire de Pharmacologie, Centre Hospitalier Universitaire (Angers, France).

Pharmacokinetic evaluation of pemetrexed and total platinum-concentration–time data was performed using non-compartmental methods with WinNonlin, version 3.1, pharmacokinetic software (Pharsight, Cary, NC, USA). Drug interaction was assessed using NONMEM version V (Globomax, Hanover, MD, USA) to compare the concentration–time data from the current study with those from previously conducted studies for pemetrexed and oxaliplatin when each was administered as monotherapy.

Patients who received at least one dose of pemetrexed and oxaliplatin were evaluated for response. Tumor response was assessed every other cycle, according to Southwest Oncology Group criteria [29], and based on measurements of initial target lesions using the same method as that used at baseline. Responses were assessed by independent review. A responder was defined as any patient who exhibited a complete response (CR) or a partial response (PR), with no requirement for a confirmation of response, 1 month later in this phase I setting. The duration of a CR or a PR was defined as the time from the documentation of response until time of progression or death due to any cause.

Results

Patient characteristics

Between January 1999 and May 2000, 45 patients were enrolled in the study in three French centers. Nine patients were not treated due to protocol violations (seven with plasma homocysteine levels > 12 μmol/l, one with hemoglobin < 9 g/dl, and one with albumin < 2.5 g/dl and hemoglobin < 9 g/dl). Thirty-six patients were assessable for toxicity and 34 were evaluable for response (two patients were not assessed due to a lack of bidimensional measurable disease). Patient characteristics at baseline for the 36 patients who received study treatment are summarized in Table 1. The most common previous chemotherapeutic agents included cisplatin in 44% of patients and 5-FU in 50% of patients.

Maximum tolerated dose

No DLT was observed at dose levels 1 (pemetrexed 300 mg/m² plus oxaliplatin 85 mg/m²) to 5 (pemetrexed 500 mg/m² plus oxaliplatin 120 mg/m²), and only five of the 16 patients enrolled at dose level 6 (pemetrexed 500 mg/m² plus oxaliplatin 130 mg/m²) manifested DLT (Table 2). Thus, the MTD was not reached at the highest dose level. The DLTs included two patients with febrile neutropenia, two with grade ≥3 diarrhea (one grade 3, one grade 4) and one with grade 3 paresthesia.

One toxic death occurred at the highest dose level after the second cycle. The patient (cervical carcinoma) exhibited...
severe aplasia with febrile neutropenia and grade 4 hemorrhage, and died 1 month later with confirmation of progressive disease. As the MTD was not reached at the highest dose level and because a toxic death occurred at this dose level after cycle 1 (DLTs recorded in cycle 1 only), the next lower dose level (dose level 5) was considered the recommended regimen for subsequent phase II studies.

Dose administration

A total of 155 cycles were administered during the study (Table 2), with a median number of four cycles per patient (range 1–11). Eight cycles (5%) were delayed due to adverse events: three cycles at dose level 5 due to neutropenia and decreased creatinine clearance, and five cycles at dose level 6 due to occlusive syndrome, anemia, thrombocytopenia and fever. There were 14 (9%) dose reductions of pemetrexed and 17 (10.9%) dose reductions of oxaliplatin, primarily due to leukopenia and paresthesia, respectively. Most dose reductions occurred at dose levels 5 and 6. No doses were omitted.

Toxicity

Myelosuppression was the major side-effect experienced throughout the study (Table 3). Overall, 21 (58%) patients experienced grade 3–4 neutropenia, with grade 4 episodes observed in nine (25%) patients. Grade 3–4 leukopenia occurred in 17 (47%) patients, with grade 4 episodes observed in three (8%) patients. Febrile neutropenia requiring hospitalization occurred in two (6%) patients. No patient received leucovorin or G-CSF. Grade 3–4 anemia occurred in seven (19%) patients and grade 3–4 thrombocytopenia occurred in eight (22%). Although thrombocytopenia necessitated platelet transfusion in three patients, no episodes of thrombocytopenia were associated with serious bleeding events.

The most common non-hematologic events were related to gastrointestinal toxicity (nausea, vomiting and diarrhea) and neurotoxicity (paresthesia). The most frequently reported grade 3/4 toxicities (in >10% of patients) included nausea (grade 3 only, 17%), diarrhea (14%), vomiting (11%) and neutromotor toxicity (grade 3 only, 11%). Twenty-one (58%) patients experienced episodes of fatigue (13 moderate and eight severe) that were considered possibly to be related to the study drug, but there was no evidence of cumulative fatigue. Grade 3 neurosensory toxicity occurred at the highest dose level in two patients, and grade 3 neuromotor toxicity occurred in six patients from dose levels 4–6. Grade 3 and 4 transaminase elevations were transient and not dose-limiting.

Pharmacokinetic results

Selected pemetrexed and total platinum pharmacokinetic parameters are presented in Table 4. Population pharmacokinetic comparison of pemetrexed concentration–time data following pemetrexed in combination with oxaliplatin with those following pemetrexed administered alone showed no statistically significant difference between the two dosage regimens in pemetrexed pharmacokinetics. The pharmacokinetic parameter results combined with the consistency between plasma concentration–time data from the current study and previous monotherapy results indicate a lack of drug interaction between pemetrexed and oxaliplatin when given in combination.

### Table 3. Number of patients with maximum NCI-CTC grade 3 and 4 hematologic toxicity by dose level (n = 36)

<table>
<thead>
<tr>
<th>Pemetrexed/oxaliplatin (mg/m²)</th>
<th>No. of patients treated</th>
<th>Leukopenia 3</th>
<th>Leukopenia 4</th>
<th>Neutropenia 3</th>
<th>Neutropenia 4</th>
<th>Thrombocytopenia 3</th>
<th>Thrombocytopenia 4</th>
<th>Anemia 3</th>
<th>Anemia 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>300/85</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>400/85</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>400/100</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>500/100</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>500/120</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>500/130</td>
<td>16</td>
<td>8</td>
<td>1</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

NCI-CTC, National Cancer Institute common toxicity criteria.

### Table 4. Pharmacokinetic parameters for pemetrexed and oxaliplatin

<table>
<thead>
<tr>
<th></th>
<th>Mean (range)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pemetrexed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(500 mg/m², n = 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</td>
<td>102 (67.9–132)</td>
<td>18.3</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–1&lt;/sub&gt; (µg·h/ml)</td>
<td>145 (91.7–240)</td>
<td>27.0</td>
</tr>
<tr>
<td>CL (ml/m)</td>
<td>96.9 (56.9–156)</td>
<td>28.9</td>
</tr>
<tr>
<td>V&lt;sub&gt;ss&lt;/sub&gt; (l)</td>
<td>12.4 (7.37–20.9)</td>
<td>28.3</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>3.53 (2.64–4.91)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Oxaliplatin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(130 mg/m², n = 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</td>
<td>2.85 (2.22–3.98)</td>
<td>15.1</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–1&lt;/sub&gt; (µg·h/ml)</td>
<td>235 (164–300)</td>
<td>17.4</td>
</tr>
<tr>
<td>CL (ml/m)</td>
<td>15.1 (10.9–23.4)</td>
<td>27.8</td>
</tr>
<tr>
<td>CL (ml/m²)</td>
<td>9.48 (7.22–13.2)</td>
<td>18.8</td>
</tr>
<tr>
<td>V&lt;sub&gt;ss&lt;/sub&gt; (l/m²)</td>
<td>126 (84.4–172)</td>
<td>21.1</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>202 (162–240)</td>
<td>–</td>
</tr>
</tbody>
</table>

n, number of patients; CV, coefficient of variation; C<sub>max</sub>, maximum plasma concentration; AUC, area under the curve; CL, plasma clearance; V<sub>ss</sub>, steady state volume of distribution; t<sub>1/2</sub>, half-life expressed as harmonic mean.
Tumor response

Five objective antitumor responses (best response) were observed at dose levels 5 (pemetrexed 500 mg/m² plus oxaliplatin 120 mg/m², one PR) and 6 (pemetrexed 500 mg/m² plus oxaliplatin 130 mg/m², four PRs). Responses were observed in patients with breast cancer (response duration 13 weeks), rectal cancer (13 weeks), stomach cancer (12 weeks), cholangiocarcinoma (10 weeks) and adenocarcinoma of unknown primary site (response duration not assessable). All but one responder had received at least one previous course of chemotherapy for metastatic disease, with some including 5-FU. Eighteen patients achieved stable disease, which was mainly observed in colon, ovarian, and head and neck cancers across all dose levels. One patient with prostate carcinoma who progressed under previous chemotherapy and hormonotherapy had improved performance status and decreased prostate-specific antigen levels at the highest dose level. One patient with liver metastases of adrenal carcinoma had a decreased tumor volume at the third dose level, which permitted complete surgical resection and a disease-free interval of 10 months.

Discussion

This phase I study demonstrated that the combination of pemetrexed plus oxaliplatin is feasible and can be safely administered every 21 days in patients with solid tumors. Toxic effects were predictable, reversible and manageable, with neutropenia being the primary toxicity and no unexpected toxicity observed. As the MTD was not reached at the highest dose level and because a toxic death occurred at this level, the investigators recommended the more conservative regimen of the next lower dose level (pemetrexed 500 mg/m² plus oxaliplatin 120 mg/m²) for future phase II studies.

The hematologic toxicity encountered with the pemetrexed–oxaliplatin combination in the present study is similar to that observed with pemetrexed alone. Despite the frequent occurrence of grade 3 and 4 neutropenia, only two patients developed neutropenic fever. Likewise, thrombocytopenia occurred, but was not associated with serious bleeding. In addition, no patient required leucovorin or G-CSF support. One patient who had metastatic cervical carcinoma exhibited severe aplasia associated with fever and grade 4 hemorrhage after receiving two cycles of pemetrexed at the highest dose level (500 mg/m² plus oxaliplatin 130 mg/m²). The patient died 1 month later and progressive disease was confirmed. She was pretreated with cisplatin/5-FU and curative pelvic radiation.

No cumulative fatigue was observed in the present study. A common toxicity observed in early clinical trials of pemetrexed has been the development of an erythematous macular rash [8]. The incidence of skin toxicity in the current study was 19% (three and four patients with grade 1 and 2 toxicity, respectively), with no grade 3 or 4 events reported. The low frequency and severity of rashes is probably due to the prophylactic use of dexamethasone, as demonstrated in previous phase I and II studies.

Other severe non-hematologic toxicities previously described with pemetrexed include stomatitis, diarrhea, vomiting and infection [8]. In the present study, grade 3 and 4 diarrhea occurred, mainly at the highest dose level, in 8% and 6% of patients, respectively. Severe stomatitis was infrequent, with only two patients developing grade 3 toxicity. Nausea and vomiting episodes were well controlled with standard antiemetic treatments and occurred only at the highest dose level. As observed in previous clinical studies with pemetrexed and other antifolate drugs, transient grade 3 and 4 elevations of transaminases were observed but were not dose-limiting.

The addition of folic acid and vitamin B₁₂ decreases the frequency of severe clinical toxicities of pemetrexed and allows this agent to be applied clinically with a markedly improved safety margin [30]. Niwizka et al. observed that high baseline homocysteine levels (>11.5 µmol/l), which reflect patient folate status, were closely related to an increased risk of grade 4 neutropenia and thrombocytopenia, as well as grade 3–4 diarrhea and mucositis [31]. The satisfactory functional folate status of the patients included in the present study (baseline homocysteine levels <12 µmol/l) likely contributed to the manageable safety profile of the combination. Recently, the routine addition of daily low-dose folic acid and vitamin B₁₂ has been instituted in all clinical trials with pemetrexed.

The dose-limiting and main toxicity for oxaliplatin monotherapy is a sensory peripheral neurotoxicity that results in paresthesia and dysesthesia with increased cumulative doses. In the present study, the known neurotoxicities of oxaliplatin did not increase with the addition of pemetrexed compared with those reported in previous studies [32]. No overlapping toxicities between pemetrexed and oxaliplatin administered every 21 days were observed, allowing the use of full doses of both compounds.

Population pharmacokinetic comparison of pemetrexed concentration–time data following pemetrexed–oxaliplatin combination therapy and those following pemetrexed administered alone showed no statistically significant difference between pemetrexed pharmacokinetics of the two regimens. Therefore, oxaliplatin administration does not alter the pharmacokinetics of pemetrexed. Pemetrexed total plasma clearance, steady-state volume of distribution, and half-life for pemetrexed given in combination with oxaliplatin as in the current study are consistent with previously reported pharmacokinetic results for single-agent administration [9]. Total platinum clearance, steady-state volume and terminal half-life were similar for all oxaliplatin doses. Published estimates of terminal elimination half-life of total platinum vary based on assay sensitivity, sampling schedule and the complexity of the pharmacokinetic model. With a minimum assay sensitivity of 3 ng/ml and plasma collected out to 20 days (collected for PK analysis past day 20 starting the day of drug administration), the terminal elimination half-life of total platinum in plasma for the current study, evaluated using non-compartmental analyses, was approximately 7–12 days (median ~9 days). This range corresponds to values (~11 days (range 8–12)) obtained in similarly designed studies utilizing more sensitive
assay methods for total platinum and analyzed using a three-compartment pharmacokinetic model [32–34]. The model-predicted central tendency and 95% tolerance interval for the oxaliplatin concentration–time profile from the current study is consistent with previously reported results [33]. Therefore, pemetrexed co-administration did not appear to alter the pharmacokinetics of oxaliplatin over the range of doses studied.

Although tumor response was not the primary end point of this study, the antitumor activity was very encouraging. Objective responses were observed in a variety of tumors, including tumors traditionally resistant to chemotherapy such as cholangiocarcinoma and stomach carcinoma. All but one responder had received at least one previous chemotherapy regimen for metastatic disease. Disease stabilization occurred in 58% of the non-responding patients, including one patient with prostate cancer who had improved performance status and decreased prostate-specific antigen level.

In conclusion, the combination of pemetrexed and oxaliplatin administered every 21 days is well tolerated with a manageable safety profile and no overlapping toxicity in patients with solid tumors. The investigator-recommended regimen for further phase II studies is pemetrexed 500 mg/m² plus oxaliplatin 120 mg/m² every 21 days, a regimen that is well tolerated even without vitamin supplementation in patients selected for low homocysteine levels (<12 μmol/l). There is no evidence of a pharmacokinetic interaction between pemetrexed and oxaliplatin over the dose ranges of 300–500 mg/m² and 85–130 mg/m², respectively.

Acknowledgements

The authors wish to thank David Radtke, BS, Assistant Senior Pharmacokineticist, for his assistance with the analyses and for writing the pharmacokinetics sections of this manuscript, and Mary Alice Miller, PhD, Scientific Communications Consultant, and Noelle Gasco, Scientific Communications Associate, for their editorial assistance. This study was conducted with research support from Eli Lilly and Co.

References

24. Machover D, Diaz-Rubio E, de Gramont A et al. Two consecutive phase II studies of oxaliplatin (L-OHP) for treatment of patients with
advanced colorectal carcinoma who were resistant to previous treatment with fluoropyrimidines. Ann Oncol 1996; 7: 95–98.


