Gemcitabine (GEM) as a single agent, or in combination with other chemotherapeutic drugs, has shown documented efficacy in a variety of solid tumor malignancies (1–5). GEM is the current cornerstone of treatment for pancreatic cancer (1). It is also used for bladder, non–small cell lung, breast, and ovarian cancer (2–5).

Imatinib mesylate (IM) is an inhibitor of bcr-abl, platelet-derived growth factor receptor (PDGFR) and the c-kit tyrosine kinase (6). Because of its inhibition of bcr-abl, IM has been approved by the Food and Drug Administration for the treatment of patients with Philadelphia chromosome–positive chronic myelogenous leukemia in chronic or accelerated phase, or in blast crisis (7). Because of its inhibition of c-kit (8), IM is also Food and Drug Administration–approved for the treatment of gastrointestinal stromal tumors. IM also has clinical efficacy in certain myeloproliferative disorders (9) and dermatofibrosarcoma protuberans (10), which have been shown to have dysregulated cell signaling associated with PDGFR-β tyrosine kinase activity. The IC50’s of IM for PDGFR tyrosine kinase and c-kit are ~0.1 μmol/L (11), which is relatively low.

Other tumors that may express c-kit, depending on technique and tumor subtype, include acute myelogenous leukemia, angiosarcoma, Ewing sarcoma, seminoma, melanoma, small cell and non–small cell lung cancer, adenoid cystic tumors of the salivary glands, chromophobe and oncocytoma-type renal cancers, medullary and phylloides breast tumors, and follicular carcinoma of the thyroid (12, 13). PDGFR may be expressed on pancreatic cancer, glioblastoma, meningioma, mesothelioma, and prostate cancer among others as well as on tumor pericytes and in tumor stroma (14, 15).

PDGFR is a mediator of interstitial fluid pressure (IFP). Increased IFP, present in malignancies, has been postulated to interfere with drug uptake. Preclinical data from Pietras showed that IM combined with paclitaxel decreased tumor IFP and was more effective in the treatment of KAT-4 tumors in vivo than either agent alone (16). Similarly, IM combined with 5-fluorouracil lowered tumor IFP and was more effective in treating rats with PROb colon cancer than either agent alone. Thus, IM, possibly by inhibiting PDGFR activity, may permit improved drug uptake and efficacy.

Abstract

Purpose: Preclinical data shows improvements in response for the combination of imatinib mesylate (IM, Gleevec) and gemcitabine (GEM) therapy compared with GEM alone. Our goals were to determine the maximum tolerated dose of GEM and IM in combination, the pharmacokinetics of GEM in the absence and in the presence of IM, and IM pharmacokinetics in this combination.

Patients and Methods: Patients with refractory malignancy, intact intestinal absorption, measurable/evaluable disease, adequate organ function, Eastern Cooperative Oncology Group PS 0-2, and signed informed consent were eligible. Initially, treatment consisted of 600 mg/m² of GEM (10 mg/m²/min) on days 1, 8, and 15, and 300 mg of IM daily every 28 days. Due to excessive toxicity, the schedule was altered to IM on days 1 to 5 and 8 to 12, and GEM on days 3 and 10 every 21 days. Two final cohorts received IM on days 1 to 5, 8 to 12, and 15 to 19.

Results: Fifty-four patients were treated. IM and GEM given daily at 500 to 600 mg/m² on days 1, 8, and 15 produced frequent dose-limiting toxicities. With the modified scheduling, GEM given at 1,500 mg/m²/150 min was deliverable, along with 400 mg of IM, without dose-limiting toxicities. Three partial (laryngeal, renal, and mesothelioma) and two minor (renal and pancreatic) responses were noted at GEM doses of 450 to 1,500 mg/m². Stable disease >24 weeks was seen in 17 patients. CA19-9 in 7 of 10 patients with pancreatic cancer was reduced by ~90%. IM did not significantly alter GEM pharmacokinetics.

Conclusion: The addition of intermittently dosed IM to GEM at low to full dose was associated with broad antitumor activity and little increase in toxicity.

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Received 4/13/07; revised 6/22/07; accepted 7/17/07.

Grant support: Novartis Pharmaceuticals Corporation.

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Conclusion: The addition of intermittently dosed IM to GEM at low to full dose was associated with broad antitumor activity and little increase in toxicity.
The combination of IM and GEM has shown activity in an orthotopic nude mouse pancreatic cancer model (17). Hwang et al. evaluated the expression of PDGF ligands and receptors in clinical specimens of human pancreatic adenocarcinomas and determined the therapeutic effect of two different doses of IM on human pancreatic carcinoma cells growing in the pancreas and liver of nude mice. Tumors of mice treated for 4 weeks with IM alone were not significantly smaller than controls. Tumors of mice treated with a lower dose of GEM plus IM were >70% smaller than tumors in control mice and 36% smaller than those in mice treated with GEM only (P < 0.0002 and P < 0.04, respectively). Tumors from mice treated with the combination of IM and GEM had decreased expression of activated PDGFR-α and PDGFR-β, decreased mean vessel density, decreased cell proliferation, and increased apoptosis of tumor cells. Given this preclinical activity and the sensitivity of a wide variety of tumors to GEM, we designed a phase I study with the goal of identifying the doses and schedules of both drugs that could be used in combination.

A previous phase I study (18) of the combination of GEM and IM had used weekly GEM administered by 30-min infusion at two dose levels: 800 mg/m² of GEM on days 1, 8, and 15 every 28 days plus 400 mg of IM daily, and 700 mg/m² of GEM on days 1 and 8 every 21 days and 300 mg of IM daily. Two of the first three patients in the initial cohort developed significant neutropenia. The subsequent reduced dose cohort of GEM included four patients each with only one prior chemotherapy regimen. In that cohort, one patient developed grade 3 thrombocytopenia and one, grade 3 fatigue. No patient had a response to treatment and the study was terminated. However, gemcitabine delivered at a fixed-dose rate (FDR) infusion of 10 mg/m²/min has been suggested as being more effective than when administered by 30 min infusion (19, 20). Data from a randomized phase II study of patients with pancreatic cancer that compared weekly 1,500 mg/m² of GEM...
Patients and Methods

Eligibility. Adult patients with a refractory solid malignancy, intact intestinal absorption, measurable or evaluable disease, adequate hepatic, renal and hematologic function, Eastern Cooperative Oncology Group PS 0-2, and survival time estimated to be >3 months were eligible. As the trial progressed, patients with more than two prior chemotherapy regimens for metastatic disease, marrow involvement, or progressive disease were excluded if two or more of the following criteria were present: history of irradiation to >25% of the bone marrow, brain metastasis, or prior dose level (if only three patients were previously treated at that prior dose).

The maximum tolerated dose was either (a) that dose level at which no more than one patient experienced DLT and with the next higher level having had two patients with a DLT, or (b) that dose level in which two or five patients experienced DLT in the absence of lower dose DLT.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. All patients receiving one dose of protocol therapy were evaluable for toxicity. DLT was defined as the occurrence during the first cycle of therapy of grade 3 to 4 non-hematologic toxicity (including nausea and vomiting that could not be controlled with oral medication); grade 4 hematologic toxicity that occurred during treatment or within 1 week of treatment completion and lasting >7 days; omission or delay of treatment for toxicity of two or more doses in a cycle; or delay in initiation of a treatment cycle beyond the mandated 2 weeks.

Pretreatment evaluations. Baseline evaluations included history, complete physical examination, Eastern Cooperative Oncology Group performance status, CBC with platelet count, serum chemistries and electrolytes, chest X-ray, EKG, and tumor markers, if indicated. In addition to these evaluations, imaging studies (computed tomography or magnetic resonance imaging) of the sites of measurable disease were done.

Treatment schema. GEM was administered by FDR infusion (10 mg/m²/min). Patients were treated at 14 dose levels starting at 600 mg/m² on days 1, 8, and 15 every 28 days. Due to toxicity, the GEM dose was decreased and the schedule altered to 450 mg/m² on days 3 and 10 every 21 days and, subsequently, escalated over nine dose levels to 1,500 mg/m² on days 3 and 10 every 21 days. IM administration started at 300 mg daily and was decreased to 300 mg/d on days 1 to 5 and 8 to 12, and then escalated to 400 mg/d on days 1 to 5 and 8 to 12 every 21 days. To increase imatinib exposure, the final two cohorts received 400 mg/d of IM on days 1 to 5, 8 to 12, and 15 to 19, and 1,200 or 1,500 mg/m² of GEM, respectively. In the first cycle only, to facilitate pharmacokinetic analysis, patients received gemcitabine on day 3 and 10 and IM only on days 8 to 12. Because 1,500 mg/m² weekly is a commonly used dose for FDR GEM (21), we chose not to escalate GEM beyond 1,500 mg/m². IM was not escalated beyond 400 mg/d.

Patients were assessed for toxicity weekly and for disease regression or progression after every two cycles. All patients receiving any treatment were considered evaluable for response. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (23).

Pharmacokinetics. Heparinized blood samples (5 mL) were collected in 7 mL tubes containing tetrahydrouridine (0.7 mg) before GEM infusion, at the end of infusion, and at 10, 30, 60, 120, 180, and

Table 3. Pharmacokinetic parameters of gemcitabine alone (day 3) and in the presence of imatinib (day 10)

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>Cmax (µg/mL)</th>
<th>AUC (µg·min/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 3</td>
<td>Day 10</td>
</tr>
<tr>
<td>450 (n = 2)</td>
<td>8.2 ± 2.8</td>
<td>11.5 ± 2.7</td>
</tr>
<tr>
<td>500 (n = 2)</td>
<td>16.4 ± 2.2</td>
<td>17.7 ± 2.3</td>
</tr>
<tr>
<td>600 (n = 3)</td>
<td>11.7 ± 5.0</td>
<td>14.5 ± 7.7</td>
</tr>
<tr>
<td>700 (n = 5)</td>
<td>9.9 ± 4.9</td>
<td>13.8 ± 5.5</td>
</tr>
<tr>
<td>800 (n = 3)</td>
<td>13.4 ± 2.8</td>
<td>14.6 ± 1.8</td>
</tr>
<tr>
<td>900 (n = 3)</td>
<td>17.9 ± 6.6</td>
<td>15.7 ± 7.9</td>
</tr>
<tr>
<td>1,000 (n = 3)</td>
<td>9.9 ± 1.3</td>
<td>11.6 ± 4.9</td>
</tr>
<tr>
<td>1,200 (n = 5)</td>
<td>13.4 ± 2.8</td>
<td>15.6 ± 0.9</td>
</tr>
<tr>
<td>1,500 (n = 5)</td>
<td>14.2 ± 3.4</td>
<td>13.1 ± 1.7</td>
</tr>
</tbody>
</table>

Abbreviations: Cmax, maximum concentration; AUC, area under the concentration-time curve; CL, clearance; Vss, volume of distribution steady state; t1/2, half-life; PK model, noncompartmental.
240 min. On the day of the second GEM infusion (concurrent with IM), blood samples were collected at the end of infusion, and 10, 30 min, 60, 120, 240 min, and 24 and 48 h after the end of the GEM infusion. The samples were centrifuged at 1,000 g for 10 min at 4°C, and the resulting plasma was separated and stored at -80°C until analysis. GEM in plasma was analyzed using a validated high-performance liquid chromatography method (24). Briefly, control drug-free plasma containing known concentrations of GEM and difluoro-deoxyuridine were used to prepare the standard curve. Standard plasma and patient plasma (300 µL) were mixed with the internal standard (5-bromo-deoxyoxuridine), deproteinized with 1,200 µL of cold methanol/ acetonitrile (1:1), and centrifuged at 19,000 x g for 15 min at 4°C. The resulting supernatant was dried under vacuum/air-dried and the residue was reconstituted in mobile phase (described below) and centrifuged again at 19,000 x g for 10 min at 4°C.

The high-performance liquid chromatography system consisted of a Hitachi 7100 series (Hitachi High Technologies, Inc.) solvent delivery system (L7100) fitted with a Waters (Waters Corp.) C18 guard column and YMC ODS AQ C18 analytical column (4.6 x 250 mm, 5 µm). Samples were eluted with an isotropic mobile phase consisting of 15 mmol/L of phosphate buffer (pH 3.0)/methanol/acetonitrile (97:1.2 v/v/v) that was pumped at a flow rate of 1 mL/min. Column eluate was monitored at 269 nm with a UV absorbance detector (L7400), and detector output was integrated simultaneously using a Hitachi Multi-System Manager Software version 4.1. The retention times of gemcitabine, difluoro-deoxyuridine, and the internal standard were 12, 30, and 33 min, respectively. Standard curves were constructed by plotting the peak height ratio of GEM to internal standard against GEM concentration. The concentrations of GEM in the patient plasma were calculated from the standard curve by linear regression analysis. No weighting was used. The lower limit of quantitation for GEM was 60 ng/mL. The assay for GEM was linear from 50 ng/mL to 10 µg/mL. Model-independent, noncompartmental analysis (WinNonlin, version 2.1; Pharsight Corp.) was used to estimate the following pharmacokinetic parameters: area under the concentration versus time curve (AUC), elimination half-life ($t_{1/2}$), total body clearance (CL), and volume of distribution (Vss). To determine whether GEM pharmacokinetic parameters were altered in the presence of IM, a two-way ANOVA model was used to compare the pharmacokinetic parameters between days 10 and 3, where $P < 0.05$ was considered to be significant. Plasma concentrations of IM and its major metabolite, CGP74588, were quantitated with a previously published, validated liquid chromatography-mass spectrometry assay (25).

### Results

Between January 2003 and October 2005, 54 patients were enrolled into the study. Patient characteristics are listed in Table 1. The tested doses and the number of patients entered at each dose and toxicity are listed in Table 2. DLTs were noted in four of the first five patients treated at the initial 600 mg/m² and the subsequent 500 mg/m² GEM dose. These consisted of grade 3 liver function test abnormalities, grade 3 neuropathy, grade 3 intractable nausea and vomiting, and protracted myelosuppression (grade 3 neutropenia and grade 3 thrombocytopenia) causing omission of 2 weeks of therapy. Despite these toxicities, both patients with pancreatic cancer had a dramatic decrease in CA 19-9. A third patient with adrenal cancer, previously progressive on three different chemotherapy regimens, had disease stabilization. The severity of toxicity was unexplained and seemed more related to GEM, despite the low dose of GEM delivered.

Because we suspected that IM enhanced GEM toxicity, we altered the schedule of IM from daily to a bracketed dosing on days 1 to 5 and 8 to 12 along with gemcitabine on days 3 and 10 every 21 days. With this bracketed schedule of IM, the only DLT was a grade 4 neutropenia that was noted in one patient at dose level 10A (GEM 1,500/IM 400). Therefore, a maximum tolerated dose was not reached using IM at 400 mg in a bracketed schedule and FDR GEM, up to the previously used dose of 1,500 mg/m².

Non–dose-limiting neutropenia occurred frequently. Although most patients could be treated every 21 days, four patients experienced treatment delays, and nine patients had dose reductions due to hematologic toxicity. Liver dysfunction led to dose reductions and dose delays in five and two patients, respectively. Other toxicities included fatigue, nausea, anemia, and pleural effusion.

Four out of 10 patients with lung cancer and one out of six patients with renal cancer developed or had recurrent pleural effusions. Effusions occurred both at 300 and 400 mg doses of IM. One patient had an effusion at the time of trial entry and the remaining patients developed effusions 6 to 32 weeks after trial entry. Ultimately, recurrent pleural effusions caused three patients with lung cancer to be removed from the study. None of these effusions were classified as DLTs, as none presented during the first cycle of treatment. Most of these effusions were exudative in nature with negative cytology, although malignancy could not be entirely excluded. IM is associated with fluid retention, and could be a contributing, if not causative, factor (26, 27).

One patient, with stable adrenal cancer, developed apparent hemolytic-uremic syndrome following 40 weeks of treatment. The anemia and thrombocytopenia resolved but the patient had residual renal dysfunction with a serum creatinine of 2.5 mg/dL.
Pharmacokinetics. As reported previously, there was a dose-dependent linear increase in plasma GEM AUC (refs. 28, 29; Fig. 1). GEM AUC measured during imatinib treatment (day 10) showed a small but statistically insignificant increase relative to the AUC measured in the absence of imatinib (day 3; Table 3). The mean clearance (1,078 ± 216, 941 ± 241 mL/min), $t_{1/2}$ (18.6 ± 6, 17.5 ± 4 min), and volume of distribution (60.2 ± 22, 52.9 ± 2.5 L) of GEM were also not statistically different before and during IM coadministration. IM pharmacokinetic assessments were confounded by the variable times at which patients took this oral medication, on days 8 and 9, and prior to day 10 of GEM infusion. IM pharmacokinetic data were available for 22 patients ingesting their day 10 IM dose, concurrent with the initiation of the GEM infusion. The mean ± SD trough IM concentration for patients receiving 400 mg/d of IM was 1,561 ± 534 ng/mL; the mean ± SD $C_{\text{max}}$ was 5,073 ± 1,993 ng/mL and the mean ± SD $T_{\text{max}}$ was 4 ± 1 h. For CGP74588, a metabolite of IM, the mean ± SD trough was 367 ± 167 ng/mL; the mean ± SD $C_{\text{max}}$ was 1,068 ± 532 ng/mL and the mean ± SD $T_{\text{max}}$ was 3 ± 1 h.

Responses. Three partial (laryngeal, renal, and mesothelioma; Table 4) and two minor (renal and pancreatic cancer) responses were noted at gemcitabine doses of 450 to 1,500 mg/m². For all patients, the median duration of therapy was 14 weeks with a range of 1 to 102 weeks. The median duration of therapy for the six patients with renal cell carcinoma was 44 weeks. The patient, who enjoyed the longest duration of stable disease (102 weeks), had renal cell carcinoma previously treated with four regimens including IFN, donor lymphocyte infusion, and two phase I agents. Seventeen (32%) patients had stable disease in excess of 24 weeks. Five of these patients had renal cell carcinoma, two had non–small cell lung cancer, two had mesothelioma, and one patient each had ovary, vagina, cervix, duodenal, gastric, pancreas, and breast malignancies. Seven of 10 patients with pancreatic cancer treated with initial elevated CA19-9 had 88% to 90% reductions in CA19-9, although long-duration stable disease was not noted. The duration of treatment with GEM-IM therapy did not depend on GEM dose, as patients at the doses of GEM below the commonly accepted weekly dose of 1,000 mg/m² had some of the most protracted times on study as depicted in Fig. 2.

Discussion

This phase I study was designed to establish the maximum tolerated dose of GEM combined with IM for patients with relapsed or refractory solid malignancies and to assess GEM and IM pharmacokinetics in those patients. The addition of daily
IM to low-dose weekly GEM yielded tumor response but caused unexpected and severe toxicities. Clinically, the toxicities were among those expected with GEM treatment, but would not have been expected at the low doses of GEM used. Because our pharmacokinetic data indicated that IM did not affect GEM pharmacokinetics, we postulated that IM might, in some way, enhance GEM or GEM-triphosphate exposure in normal host tissues. Therefore, we limited IM exposure to the 5 days bracketing each gemcitabine infusion. With this more limited IM exposure, the toxicity was much decreased allowing continued treatment and GEM escalation to full dose. IM pharmacokinetics were consistent with the literature (30, 31).

Our study differed from a similar study by George et al., which used a 30-min infusion of GEM and daily imatinib. In that study, a second dose-reduced cohort had, like ours, received only minimal prior treatment. Yet toxicity was severe, prompting the study’s closure. As GEM using 30-min infusions is likely to be better tolerated with less myelosuppression, it seems that our improved tolerance was related to the use of “bracketing” GEM.

Since initiating our study, multiple trials have shown IM to have little single-agent activity against a variety of solid tumors that express either c-kit or PDGFR. In particular, no antitumor activity has been seen in phase II studies involving patients with small cell lung, pancreas, prostate, germ cell, melanoma, orovary, or breast cancer (32–40).

As noted previously, preclinical data suggests an alternative mechanism by which IM could affect malignancy. The tumor microenvironment is PDGFR-rich, and activation of PDGFR has been implicated in playing an important role in elevating the IFP (38). High IFP, in turn, could decrease the uptake of chemotherapeutic drugs (41). By inhibiting PDGFR, IM may decrease IFP, and greater entry of anticancer drugs into the cell (40, 42). However, this effect may be delicately concentration- and time-dependent. In a study of the epothilone EPO906 in combination with IM for the treatment of anaplastic thyroid tumors in severe combined immunodeficiency mice, Pietras noted maximum drug uptake only when IM was initiated 2 days prior to and continued at the time of EPO906 administration (43). No increased uptake of EPO906 was noted if IM was halted prior to EPO906 administration or if IM was administered only the day prior to and on the day of EPO906 treatment. Maximum efficacy occurred when IM was given daily or for 3 days prior to EPO906 administration.

Decreased IFP resulting in increased drug uptake may help explain the tumor control seen in our study. Antitumor activity (response or stabilization) occurred using doses of GEM as low as 450 mg/m², and was noted in patients with diverse cancers including laryngeal, pancreas, adrenal, renal, lung, gastric, mesothelioma, and breast cancer. Disease stabilization for 6 months was noted in ~30% of the patients, overall, including 10 of 30 patients treated at doses below the commonly used 1,000 mg/m² GEM dose. Additional studies of vascular permeability and real-time drug uptake may be helpful. A corollary study using F19 magnetic resonance spectroscopy is assessing the uptake of GEM into tumors in the absence and presence of IM (Personal communication: C. Presant, W. Wolf). These studies may help answer whether IM permits increased drug entry into a tumor.

Our study was also limited as we had chosen not to explore doses of IM beyond 400 mg or schedules of GEM at other times relative to the bracketing of IM. In retrospect, it is possible that GEM plus higher doses of IM may have been tolerable, with potential efficacy. Also, pursuant with the preclinical observation of Pietras, dosing of GEM later in each treatment week might have shown different toxicities and outcomes.

In conclusion, IM may increase the spectrum of GEM-responsive cancers. Phase II studies with GEM and IM combination are planned or initiated in pancreas, lung, breast, and renal cancer at our institution.

**Acknowledgments**

The authors gratefully acknowledge the assistance of Novelette Simmons and Dr. Ahamed Nazer for sample acquisition and preparation.

**References**


Clinical Cancer Research

Phase I and Pharmacokinetic Study of Imatinib Mesylate (Gleevec) and Gemcitabine in Patients with Refractory Solid Tumors

Yaqoob Ali, Yong Lin, Mecide M. Gharibo, et al.


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