

Satraplatin, an Oral Platinum, Administered on a Five-day Every-Five-Week Schedule: a Pharmacokinetic and Food Effect Study

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Abstract **Purpose:** The study aimed to assess the pharmacokinetic behavior of satraplatin under fasted and fed conditions, and its safety and preliminary antitumor activity in adults with advanced solid tumors.
Experimental Design: Satraplatin was administered orally at 80 mg/m² once daily with prophylactic antiemetics for 5 consecutive days every 5 weeks. Patients were randomized to receive day 1 and day 5 doses of satraplatin in either the fed or fasted state, the order being reversed for cycle 2. Pharmacokinetic sampling was done during the first two cycles. For all subsequent cycles, patients received satraplatin in the fasted state.
Results: Seventeen patients were treated with 60 total cycles of satraplatin. There was no dose-limiting toxicity during cycle 1. Severe hematologic toxicity was rare and the hematologic nadir occurred during week 4. Nausea, vomiting, and diarrhea were grade 1/2. No significant cardiac, renal, hepatic, or neurologic toxicity was observed. The hypothesis that food decreased ultrafiltrate platinum bioavailability could not be rejected, as the lower limit of the 90% confidence intervals for peak plasma concentration and area under the concentration-time curve from time 0 to 24 hours were 56.14% and 73.53%, respectively, both below the 80% bioequivalence acceptance criterion. One partial response (hormone refractory prostate cancer) and four durable stable diseases (breast, ovarian, parotid, and hormone refractory prostate cancer) were confirmed.
Conclusions: There is an effect of food on the pharmacokinetics of satraplatin, the clinical significance of which is unclear. It is recommended that satraplatin be administered in the fasting state. This 5-week interval schedule of satraplatin was well tolerated in heavily pretreated patients.

Platinum analogs form the mainstay of treatment for a number of cancers, including bladder, head and neck, lung, ovarian, and testicular cancer, and a usual first option against colorectal and esophagogastric cancer. All approved platinum anticancer drugs are administered i.v., with aggressive hydration to avoid acute nephrotoxicity in the case of cisplatin (1, 2). In addition, their efficacy is often limited by cumulative toxicity, particularly neurotoxicity and ototoxicity (1, 3, 4). Satraplatin [bisacetato-

amine-dichloro-cyclohexylamine-platinum(IV)] is a novel, orally bioavailable, platinum agent (5). It was selected from a series of oral platinum compounds because of promising pre-clinical features including *in vitro* antitumor activity, *in vivo* antitumor activity at least comparable with cisplatin and carboplatin in a diversity of murine and human tumor models, and finally its ability to partially circumvent intrinsic and acquired resistance to cisplatin (5–12).

When satraplatin was administered every three to four weeks, nonlinear pharmacokinetics, probably due to saturable absorption, were observed (13, 14). Subsequently, a daily schedule for five consecutive days was developed, with the dose utilized for phase II and III studies varying between 100 and 120 mg/m²/day (15–20). The drug has a favorable side-effect profile, with myelosuppression (neutropenia and thrombocytopenia) as the dose-limiting toxicity, and manageable nausea and vomiting (15, 17, 21, 22). Satraplatin has shown preliminary evidence of activity in lung, ovarian, and prostate cancer, and seems to have good efficacy in combination with radiation for lung and head and neck cancer (18, 22–25). Combinations with paclitaxel, docetaxel, gemcitabine, and capecitabine are also being evaluated (26).

A large 950-patient, double-blind, randomized phase III trial [Satraplatin and Prednisone against Refractory Cancer (SPARC)] has evaluated satraplatin in combination with prednisone as second-line therapy for hormone-refractory prostate cancer (HRPC;

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Received 9/30/08; revised 2/24/09; accepted 3/11/09; published OnlineFirst 5/19/09.

Grant support: GPC Biotech Inc., Princeton, NJ.

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Note: Presented in part at the 2006 Prostate Cancer Symposium, San Francisco, CA, February 24–26, 2006; and at the 42nd Annual Meeting American Society of Clinical Oncology, Atlanta, GA, June 2–6, 2006.

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doi:10.1158/1078-0432.CCR-08-2373

Translational Relevance

Satraplatin is a novel, orally bioavailable platinum agent selected from a series of platinum compounds because of promising preclinical features, including its ability to partially circumvent resistance to cisplatin.

Satraplatin has been recently reviewed in *Clinical Cancer Research* by Choy H et al. and Teicher B.A. (Current status and future prospects for satraplatin, an oral platinum analogue. *Clin Cancer Res* 2008;14:1633–8; and Newer cytotoxic agents: attacking cancer broadly. *Clin Cancer Res* 2008;14:1610–7).

This study describes for the first time the effect of food on the pharmacokinetics of satraplatin and the toxicologic and pharmacologic characteristics of satraplatin administered orally at 80 mg/m² once daily in a 5-day every-5-weeks schedule. The study also evaluated the antitumor activity in patients with refractory advanced solid tumors.

A double-blind, randomized phase III trial [Satraplatin and Prednisone against Refractory Cancer (SPARC)] has evaluated satraplatin at the described dose and schedule in combination with prednisone as second-line therapy for hormone-refractory prostate cancer. Overall survival results were presented at the 2007 American Society of Clinical Oncology annual meeting. The oral nature of satraplatin imposed the need for this food effect study, which is also the first to evaluate the dose and schedule used in the SPARC trial.

ref. 24). The oral nature of satraplatin imposed the need for this food effect study, which is also the first to evaluate the dose and schedule used in the SPARC trial of 80 mg/m² once daily for 5 consecutive days every 5 weeks. This dose was deemed to be more appropriate for previously treated HRPc patients. The principal objective of this study was to determine satraplatin pharmacokinetics under fasted and fed conditions in patients with refractory advanced solid tumors. Secondary objectives were to evaluate the efficacy and toxicity of this schedule.

Patients and Methods

Patient selection. Patients with histologically confirmed solid malignancies refractory to standard therapy or for whom no standard therapy exists were eligible. Patient entry criteria also included: age ≥18 y old; life-expectancy of ≥12 wk; an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2; no prior chemotherapy within 4 wk (6 wk for prior mitomycin C or a nitrosourea); adequate hematopoietic (hemoglobin ≥9 g/dL, absolute neutrophil count ≥1,500/μL, platelet count ≥100,000/μL), hepatic (bilirubin ≤1.5 times upper limit of normal serum aspartate aminotransferase, and alanine aminotransferase ≤3 times upper limit of normal or ≤5 times upper limit of normal if hepatic metastases present), and renal (serum creatinine ≤1.5 mg/dL) functions; measurable or evaluable disease; and no coexisting medical problem of sufficient severity to limit compliance with the study. Patients with symptomatic or unstable brain metastases, known hypersensitivity to platinum-containing compounds, or a history of any disease significantly affecting the gastrointestinal function were not enrolled. Patients of reproductive age were requested to practice adequate contraception while on treatment. All patients gave informed written consent before treatment according to federal and local institutional guidelines.

Treatment and dose reduction. Satraplatin was administered orally, on an outpatient basis, at a dose of 80 mg/m² once daily for 5 consecutive days followed by a 30-day follow-up period. Accordingly, a treatment cycle was defined as 5 wk. Antiemetic premedication included oral granisetron 1 h prior to satraplatin and 8 h postdosing on days 1 to 5 of each cycle. Dexamethasone and/or metoclopramide were used at the discretion of the investigator. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. For patients who had grade 3 or 4 hematologic toxicity ≥2 wk, neutropenia associated with fever (absolute neutrophil count <1,000/μL, fever ≥38.5°C), or grade 3 or 4 nonhematologic toxicity, the dose was reduced to 60 mg/m²/d. In patients who experienced intolerable grade 2 toxicity in subsequent cycles, in spite of symptomatic treatment, the satraplatin dose was also reduced to 60 mg/m²/d. A second dose reduction was not allowed and patients were removed from study in case of significant toxicity at 60 mg/m²/d. Inpatient dose escalation was not permitted. Erythropoietic growth factor support and blood transfusions were permitted, but myeloid colony-stimulating factors were only administered for complications of severe neutropenia, according to the American Society of Clinical Oncology guidelines.

All patients were instructed to fast from 10:00 p.m. of the evening prior to days 1 and 5 of cycles 1 and 2. For the first cycle, patients were randomized to receive the day 1 and day 5 doses of satraplatin in either the fed or fasted state and pharmacokinetics sampling was done. The fed/fasted state was reversed for the second cycle, with additional pharmacokinetics sampling. For all subsequent cycles, patients received satraplatin in the fasted state. For the fasting condition, patients fasted until 4 h post-satraplatin dosing. Water was allowed *ad lib* except for 1 h before and after study medication dosing. For the fed condition patients ate a high-fat, high-calorie breakfast adapted from the Food and Drug Administration Guidance for Industry "Food-Effect Bioavailability and Bioequivalence Studies" (27). Patients had 30 min to complete the meal and were then immediately given satraplatin (within 5 min) with tap water. Additional liquids were prohibited for 1 h after administration of the drug. During cycle 1 and cycle 2, day 1 and day 5 doses of satraplatin were administered with 240 mL (8 fluid ounces) of water. On the nonsampling days of the first two cycles and for cycle 3 and beyond, the study drug was taken on an empty stomach (no food for 1 h before until 2 h after satraplatin dose) with 120 mL to 240 mL (4–8 fluid ounces) of water.

Satraplatin was supplied by GPC Biotech Inc. as 10-mg and 50-mg capsules. The actual dose of satraplatin administered was calculated from the patient's body surface area at the beginning of each cycle and rounded to the nearest available capsule strength. Patients were instructed to self-administer satraplatin at the same time of day according to the treatment schedule. A diary that detailed the dates and times of drug administration as well as relevant events and possible toxicities was kept by each patient.

Study investigations. The baseline assessment included a complete medical history, physical examination, vital signs, ECOG performance status, complete blood count, serum biochemistry, electrocardiogram, and urinalysis. Computed tomography scans were used for assessment of the baseline tumor burden. Complete blood count was done weekly. Response assessment was carried out every two cycles with computed tomography scans, according to the Response Evaluation Criteria in Solid Tumor (RECIST; ref. 28). Prostate-specific antigen (PSA) response criteria was also used for patients with HRPc (29). Patients showing disease progression were taken off study.

Sample collection and analytical analysis: plasma pharmacokinetics. A total of 12 blood samples for satraplatin were collected on days 1 and 5 of cycles 1 and 2 at the following time points: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 10, 12, 16, and 24 h, then one sample on 8, 15, 22, and 29 d after the administration of the first dose of cycle 1 and 2. Satraplatin blood samples (7 mL) were collected in vials containing EDTA via an indwelling venous catheter and cooled immediately on ice, and then centrifuged at 2,000 × g for 10 min under refrigeration (4°C) within 30 min of

Table 1. Patient characteristics

| Characteristics | No. |
|---|------------|
| No. patients | 17 |
| Median age in y (range) | 62 (33-78) |
| Sex (M/F) | 9/8 |
| Median no. courses/patient (range) | 3 (1-9) |
| Performance status (ECOG) 0 / 1 / 2 | 3 / 13 / 1 |
| Previous therapy | |
| Chemotherapy | 17 |
| Median no. prior chemotherapy regimens (range) | 3 (1-8) |
| Prior platinum drugs* | 8 |
| Radiation therapy | 13 |
| Tumor types | |
| HRPC | 7 |
| Breast | 3 |
| Anal, parotid, Merkel cell, ovarian carcinoma, mesothelioma, leiomyosarcoma, and neuroendocrine tumor | 1 each |

*Includes cisplatin, carboplatin, and oxaliplatin.

collection. Plasma ultrafiltrate (PUF) was collected from the separated plasma using Millipore Centrifree YM-30 ultrafiltration devices. Briefly, plasma samples were centrifuged at 4°C for 20 minutes at 2,000 × g to generate PUF. The resulting plasma and PUF samples were assayed for platinum concentrations using a validated inductively coupled plasma-mass spectrometric assay. Samples were analyzed for platinum by inductively coupled plasma-mass spectrometry after dilution with 0.005% Triton X-100 in 0.5% nitric acid. The samples were analyzed without predigestion directly against matrix-matched standard solutions. Intensity as counts per second from platinum, mass 195, were measured. Terbium, mass 159, was used as an internal standard. Results were calculated from the net intensity ratio of platinum to internal standard. The assay was linear over the range of 2 to 1,000 ng/mL in plasma and from 0.5 to 500 ng/mL in PUF with a lower limit of quantitation of 2 ng/mL in plasma and 0.5 ng/mL in PUF. Concentrations of platinum in quality control samples were within 7% of nominal in plasma and within 9% of nominal in PUF.

Pharmacokinetic analysis. The pharmacokinetic data were analyzed using WinNonlin Professional 4.0.1 (Pharsight Corporation). The effect of food on satraplatin absorption was assessed using noncompartmental methods. The peak plasma concentration (C_{max}) and time at maximum concentration observed (T_{max}) were recorded as observed. The following pharmacokinetic parameters were calculated for day 1 of both treatment cycles: C_{max} , T_{max} , area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}), elimination rate constant (λ_E), and terminal elimination half-life ($t_{1/2}$); and the following pharmacokinetic parameters were calculated for day 5 of the fasted treatment cycles: C_{max} , T_{max} , λ_E , and $t_{1/2}$. For day 5 of the fasted treatment cycles, the AUC_{0-24} was calculated in order to assess the accumulation ratio of day 5: day 1 after fasted treatments over the same dosing range (i.e. 24 h). Descriptive statistics for total plasma and PUF platinum concentrations and pharmacokinetic parameters were done using SAS 8.2 (SAS Institute Inc.). The inferential statistical analysis using log-transformed data to assess the bioequivalence of satraplatin treatments after the fed and fasted states was done using SAS 8.2, following Food and Drug Administration guidelines for interpretation of data characterizing the effect of food on drug absorption (27).

Results

Seventeen patients, whose pertinent demographic characteristics are depicted in Table 1, were treated with 60 cycles of satraplatin. Eight patients had received previous treatment with

a platinum compound. All seven patients with HRPC had received prior radiation therapy and docetaxel (Table 1). The median number of cycles administered per patient was 3, and 13 patients completed at least 2 cycles of therapy. Two patients required dose reduction for toxicity after two and four cycles, respectively.

Toxicity. Myelosuppression, including neutropenia (41.2%) and thrombocytopenia (47.1%), was the principal toxicity of satraplatin. Table 2 details the number of patients with grade 3 and 4 neutropenia and thrombocytopenia. These toxicities were rarely associated with clinical sequelae, and neutropenia associated with fever only occurred during 1 of 60 cycles (1.7%), with no bleeding associated with thrombocytopenia. The hematologic nadir was late, usually during the fourth week after therapy. Treatment-related anemia (58.8%) was typically grade 1/2. Severe anemia (grade 3) occurred in 4 of 17 patients (23.5%) and 9 patients (59.2%) required RBC transfusions on at least one occasion.

The nonhematologic toxicities of satraplatin were consistent with the toxicities observed in previous studies (Table 2). The most common gastrointestinal side effects were grade 1/2 nausea (64.7%), vomiting (41.2%), and diarrhea (47.1%), and were controlled with oral therapy. Fatigue (52.9%) was reversible by the fourth week after drug administration. No significant cardiac, renal, hepatic, or neurologic toxicity was observed. Five patients received five or more cycles of therapy without significant evidence of nonhematologic cumulative toxicity.

Pharmacokinetics. Of the 13 patients who completed at least 2 cycles, 12 patients completed pharmacokinetic sampling and are included in the pharmacokinetic and statistical analyses of bioequivalence of satraplatin treatments after the fed and fasted states. All scheduled pharmacokinetic blood samples were collected and analyzed for platinum concentrations in plasma and PUF. All predose total plasma platinum concentrations on day 1 of cycle 2 were above the limit of quantification, and all were >5% of C_{max} . Few predose plasma levels for PUF platinum on day 1 of cycle 2 were observed above the limit of quantification, and all were <5% of C_{max} . The day 1 cycle 2 total plasma platinum profiles and pharmacokinetic parameters were reported and included in the descriptive statistics of pharmacokinetic parameters. However, due to high predose platinum concentrations, the statistical analysis was not done on the total plasma platinum for day 1 of fed and fasted cycles, and only PUF platinum pharmacokinetic parameters (AUC_{0-24} and C_{max}) were used in the statistical analysis to assess the bioequivalence

Table 2. Toxicity: grade 3/4 adverse events that occurred with a frequency of at least 5% all causality (maximum grade)

| Adverse event | No. of patients with toxicity/all patients (%) Grade 3 and 4 |
|-----------------------------|--|
| Leukocytes ($10^9/L$) | 4/17 (23.5) |
| Neutrophils ($10^9/L$) | 6/17* (35.3) |
| Platelet count ($10^9/L$) | 4/17 (23.5) |
| Hemoglobin (g/dL) | 4/17 (23.5) |
| Abdominal pain | 2/17 (11.8) |
| Dyspnea | 1/17 (5.9) |
| Fatigue | 1/17 (5.9) |

*One episode of neutropenic fever.

Table 3. Mean (\pm SD) plasma (total) and PUF platinum pharmacokinetic parameters during cycles 1 and 2

| Pharmacokinetic parameter (unit) | Day 1, fasted (n = 12) | Day 1, fed (n = 12) | Day 5, fasted (n = 12) |
|---|--|---|------------------------|
| | Plasma platinum (\pm SD) | | |
| C_{max} (ng/mL) | 2,24.9 (50.1) | 204.7 (56.6) | 568.5 (123.3) |
| T_{max} (h)* | 3.5 (2.0-10.0) | 7.0 (2.0-12.1) | 3.0 (1.0-15.0) |
| AUC ₀₋₂₄ (ng*hr/mL) | 4,204.9 (978.4) | 3,879.3 (1,135.6) | 11,554.0 (2,249.5) |
| λz (h ⁻¹) | 0.013206 (0.004910) | 0.012093 (0.006669) | 0.003004 (0.0005274) |
| $t_{1/2}$ (h) | 99.8 (169.5) | 83.7 (62.3) | 239.8 (58.0) |
| | PUF platinum (\pm SD) | | |
| C_{max} (ng/mL) | 56.9 (19.2) | 42.9 (16.2) | 69.4 (26.7) |
| T_{max} (h)* | 2.5 (1.0-4.0) | 4.0 (1.5-8.0) | 1.5 (0.5-8.0) |
| AUC ₀₋₂₄ (ng*hr/mL) | 466.1 (165.8) | 425.3 (112.4) | 701.3 (222.1) |
| λz (h ⁻¹) | 0.034908 (0.014598) | 0.052282 (0.020913) | 0.003504 (0.0011734) |
| $t_{1/2}$ (h) | 31.6 (38) | 16.4 (9.6) | 211.9 (55.5) |
| | Plasma platinum accumulation ratio, % [†] (95% confidence interval), n = 7 | PUF platinum accumulation ratio, % (95% confidence interval), n = 12 | |
| AUC ₀₋₂₄ (day 5)/AUC ₀₋₂₄ (day 1) | 2.99 (2.58-3.46) | 1.51 (1.37-1.66) | |

* T_{max} : Median (minimum-maximum).[†]Cycle 1 only.

after fed and fasted treatments. Because patients took study drug on days 2 through 5 in the fasted state in both treatment cycles, the day 5 fed to fasted comparison was not interpretable. Table 3 summarizes satraplatin pharmacokinetic parameters on day 1 after fasted and fed treatments and day 5 after fasted treatment. Interpatient variability was not significant in this study (coefficient of variant \sim 20%). For total plasma platinum on day 1 after fasted and fed treatments, mean C_{max} was 224.9 ng/mL and 204.7 ng/mL, respectively; mean AUC₀₋₂₄ was 4,204.9 ng*hr/mL and 3,879.3 ng*hr/mL respectively; and mean T_{max} was 3.5 hours and 7.0 hours, respectively. For PUF platinum, on day 1 after fasted and fed treatments, mean C_{max} was 56.9 ng/mL and 42.9 ng/mL respectively; mean AUC₀₋₂₄ was 466.1 ng*hr/mL and 425.3 ng*hr/mL respectively; and mean T_{max} was 2.5 hours and 4.0 hours, respectively.

The results of the ANOVA statistical analysis for bioequivalence are provided in Table 4. Figure 1 illustrates the mean (and SD) PUF platinum concentration profiles of satraplatin on day 1 after fasted and fed states. The PUF platinum pharmacokinetic parameters on day 1 fed to fasted satraplatin comparison for C_{max} and AUC₀₋₂₄ supported rejection of the hypothesis that dose administration with food increased platinum bioavailability; the 90% confidence interval (90% CI) upper limits were $<125\%$, 98.68% for C_{max} and 114.93% for AUC₀₋₂₄. The hypothesis that food decreased platinum bioavailability could not be rejected, as the lower limits of the 90% CI for C_{max} and AUC₀₋₂₄ were 56.14% and 73.53%, respectively, both lower than the 80% bioequivalence acceptance criterion.

The accumulation ratio for plasma platinum (fasted AUC₀₋₂₄ on day 5: fasted AUC₀₋₂₄ on day 1) of 2.99 (confidence interval, 2.58-3.46) was based on patients in cycle 1 only, due to the observation of high predose levels in cycle 2. The accumulation ratio for PUF platinum was 1.51 (95% confidence interval, 1.37-1.66; Table 3).

Antitumor activity. There was a confirmed partial response and other evidence of preliminary clinical activity. One patient with heavily pretreated HRPC had a confirmed partial response, according to RECIST and PSA criteria, of 12 months' duration. The patient had received radiotherapy and his prior systemic treatments included a luteinizing hormone-releasing hormone agonist, docetaxel, topotecan with estramustine and thalidomide. Two additional patients with HRPC had stable disease for six and four months, respectively. More significantly, sustained stable disease for approximately one year was seen in three patients respectively with parotid carcinoma and carboplatin-resistant breast and ovary carcinoma, all of whom had documented disease progression before enrollment.

Discussion

This study reports the effect of food on the pharmacokinetics of satraplatin administered at 80 mg/m²/day for 5 consecutive days every 5 weeks. The descriptive pharmacokinetic results in

Table 4. ANOVA analysis of PUF platinum pharmacokinetic parameters on day 1 after fed and fasted state

| Parameter | Geometric mean ratio (%) fed/fastest (90% CI), 12 patients | Intrapatient CV (%)* |
|---------------------|--|----------------------|
| C_{max} | 74.43% (56.14-98.68%) | 38.95 |
| AUC ₀₋₂₄ | 91.93% (73.53-114.93%) | 30.42 |

*Mixed model estimate of intrasubject correlation for each PK parameter was 0.

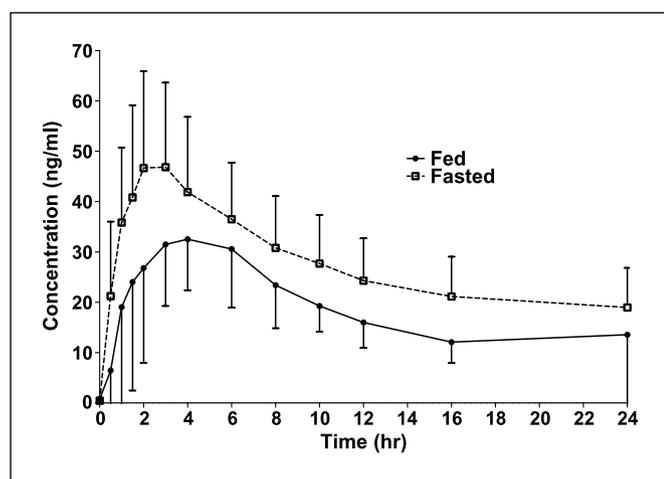


Fig. 1. Mean (SD) PUF platinum concentration profiles of satraplatin on day 1 after fasted and fed state.

the fasted state (Table 3) are consistent with those reported from other studies exploring ranges (60, 75, 100, and 120 mg/m²) that encompass this dose (13, 15, 16). Interpatient variability in the current study was not found to be significant.

To rule out an effect of food on the overall exposure of satraplatin, the 90% CIs of both C_{max} and AUC should be within the accepted bioequivalence range of 80 to 125%. Assessment of the effect of food on the pharmacokinetic of total plasma platinum was not possible due to observation of predose concentrations higher than 5% C_{max} on day 1 of cycle 2; thus only PUF platinum pharmacokinetic parameters were used in the statistical analysis. Based on this analysis, the fed/fasted geometric mean 90% CI lower limit for C_{max} of 56.14% was below the accepted bioequivalence range of 80% to 125%. Correspondingly, the fed/fasted geometric mean ratio 90% CI lower limit for AUC₀₋₂₄ of 73.53% was also below the accepted range. Thus a food effect with decreased C_{max} and AUC₀₋₂₄ by 25.57% and 8.07%, respectively, was observed after the fed treatment, indicating that satraplatin should be administered to patients in a fasted state. Further, there was accumulation of PUF platinum on day 5 compared with day 1 after fasted treatment (based on the ratio of AUC₀₋₂₄ to AUC₀₋₂₄) estimated to be 1.51 (95% confidence interval, 1.37-1.66).

When used in the 5-consecutive-day dose per cycle schedule, the dose-limiting toxicity of satraplatin has consistently been

myelosuppression (15). In this study, myelosuppression was the principal grade 3/4 toxicity of satraplatin, although rarely associated with clinical sequelae. Blood count nadirs occurred typically during the fourth week, later than after conventional alkylating agents and carboplatin (15). Consequently, the current 5-week interval schedule is more appropriate with respect to the pharmacodynamic effect on hematopoiesis. Of note, there was no cardiac, renal, hepatic, or neurologic toxicity.

Recent results of the SPARC trial in HRPC, which utilized the dose and schedule reported in this paper, showed that satraplatin plus prednisone treatment was associated with a 31% reduction in the risk of progression-free survival events (hazard ratio, 0.69; 95% confidence interval, 0.60-0.80; $P < 0.00001$). The end point of overall survival ($P = 0.80$, log-rank analysis) was not achieved. However, when adjusted for prespecified prognostic factors, there was a positive trend in overall survival observed in docetaxel-treated patients (hazard ratio, 0.78; 95% confidence interval, 0.61-0.99; ref. 30). In the present phase I study one patient with heavily pretreated HRPC had a confirmed partial response according to RECIST and PSA criteria, with five other patients having stable disease of considerable duration (4-12 months). The tolerable toxicity and the preliminary activity observed in our study seem to favor this schedule of drug delivery for future relapsed or refractory disease-oriented studies.

In conclusion, satraplatin was well tolerated at a dose of 80 mg/m² once daily for 5 consecutive days every 5 weeks. There is an effect of food resulting in a decrease of the C_{max} and AUC₀₋₂₄ of satraplatin; the clinical significance of which is unclear with respect to antitumor activity. Consequently, it is recommended that satraplatin be administered in the fasted state. The observation of preliminary antitumor activity at this dose is encouraging and provides a rationale for further phase II evaluations in relapsed or refractory carcinomas.

Disclosure of Potential Conflicts of Interest

D. Greene, M. Petrone, and F. Nathan are employed by GPC Biotech. A. Tolcher has served as a consultant for the following parties: Abraxis, Adnexus, Amgen, Anandys, Ariad Pharmaceuticals, AstraZeneca, Astellas, Biogen Idec, Centocor, Chemokine, Curis, Cytogenetics, Dendreon Corp., Eli Lilly, Enzon, Exelixis, Fibrogen, Five Prime Therapeutics, Genentech, Genetics Squared, Genta, Geron, HUYA Bioscience International, Immunogen, Johnson & Johnson, Merck, MGI Pharma, Micromet, NCI Drug Development Group, Nektar, Nereus, Nervianoms, Onyx Pharmaceuticals, Paramount Biosciences, Pfizer, Sankyo, Sanofi-Aventis, Santaris, Schering-Plough, Spectrum, Symphogen, Supergen, and Takeda.

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Clin Cancer Res 2009;15:3866-3871.

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