An open-label, dose-finding study of the combination of satraplatin and gemcitabine in patients with advanced solid tumors

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Purpose: Satraplatin is a third generation oral platinum, which has demonstrated antitumor activity. The aim of this phase I study was to determine the maximum tolerated dose (MTD) of the combination of satraplatin and gemcitabine in patients previously treated with chemotherapy and in patients without prior chemotherapy. Patients and Methods: Two separate MTDs were planned in two different patient groups (those with and without prior chemotherapy treatment). Dose escalations were planned in cohorts of three patients. Tumor measurements were obtained every two cycles. Assessment of response was performed according to Response Evaluation Criteria in Solid Tumors (RECIST criteria v.1.0). Results: Thirty subjects were enrolled. A MTD of gemcitabine 1000 mg/m² days 1 and 8 plus satraplatin 60 mg/m² days 1–3, every 21 days was determined in the prior chemotherapy group. No MTD could be determined for the no prior chemotherapy group treated with this schedule. Five patients completed 12 treatment cycles; 22 serious adverse events (SAE) were observed. Although not an entry criteria, overall confirmed response was observed in 17 (24%) evaluable patients (complete response, CR = 1 and partial response, PR = 3) and in 3/7 (43%) patients with measurable prostate cancer lesions. Conclusions: In this phase I b study, the combination of satraplatin and gemcitabine demonstrated to be safe and efficacious in particular in patients with prostate cancer.

Keywords: satraplatin, oral platinum, phase I study, prostate cancer, solid tumors, chemotherapy

INTRODUCTION

Satraplatin is a third generation oral platinum complex that has demonstrated activity against several platinum-sensitive and -resistant human tumor cell lines (Twentyman et al., 1992; Kelland et al., 1993; Mellish et al., 1995; Beale et al., 1998; Latif et al., 1999). Preclinical and clinical studies have shown that satraplatin can potentiate the effects of radiotherapy (Van de Vaart et al., 1997; Twentyman et al., 1999; Beale et al., 1998; Sessa et al., 1998; Fokkema et al., 2000; Vouillamoz-Lorenz et al., 2003; Ricart et al., 2003). In clinical studies, the most frequent dose limiting toxicity (DLT) observed with satraplatin was myelosuppression (leucopenia and thrombocytopenia; McKnagge et al., 1995, 1997; Beale et al., 1998; Sessa et al., 1998; Fokkema et al., 2000; Vouillamoz-Lorenz et al., 2003; Ricart et al., 2003; Galisky et al., 2012).

In a phase II trial of satraplatin in 39 chemo-naive patients with progressive castration-resistant prostate cancer (CRPC), 7 of 22 (32%) patients had a PSA response, toxicity was mainly hematologic, with grade 3/4 non-hematologic toxicities including transient increases in aspartate transaminase and bilirubin (Latif et al., 2005). These results led the European Organization for Cancer Research (EORTC) to initiate a phase III trial of satraplatin plus prednisone vs prednisone alone for first-line treatment of patients with CRPC (Sternberg et al., 2005). Although the target accrual was 380 patients, only 50 patients were enrolled when the study was terminated early due to a company decision. This trial demonstrated that the combination of satraplatin and prednisone resulted in a significant increase in PSA response compared to prednisone alone (33 vs 9%; $P = 0.046$), and improvement in progression-free survival (PFS; 5.2 vs 2.5 months; $P = 0.023$; Sternberg et al., 2005).

Encouraging results of this EORTC trial led to development of the SPARC (Satraplatin and Prednisone against Refractory Cancer) study (Stenberg et al., 2009). This trial was a phase III randomized double-blind study in which satraplatin plus prednisone was compared to placebo plus prednisone as second-line
treatment in patients with CRPC who had received one prior line of cytotoxic chemotherapy. The PFS was 11.1 weeks on the satraplatin and prednisone arm and 9.7 weeks on the placebo and prednisone arm ($P < 0.001$). The median time to pain progression was 66.1 weeks for satraplatin and 22.3 weeks for placebo. A PSA response was observed in 25.4 and 12.4% of patients, respectively ($P < 0.001$). Despite the improvement in PFS and the palliative effects in favor of satraplatin, overall survival (14.3 months in both arms), the preferred endpoint for regulatory approval by the FDA, for prostate cancer clinical trials as most patients have inevaluable bone disease, was not extended by satraplatin.

Gemcitabine is frequently used in the treatment of several tumor types including breast, bladder, non-SCLC, and pancreatic cancers. Activity has also been reported in biliary tract, cervical, gall bladder, and ovarian cancers. Gemcitabine has been combined with several different chemotherapeutic agents and has shown activity with platinum compounds, taxanes, anthracyclines, 5-fluorouracil, irinotecan, vinorelbine, and others (Pollera et al., 1994; Glimelius et al., 1996; Burris et al., 1997; Sternberg, 2000).

The rationale for this study was based primarily upon the general synergy between platinum compounds and gemcitabine. Simultaneous drug combination of satraplatin and gemcitabine in UM-UC-3 cells was often more effective than the individual drug treatments but overall showed less than additive effects (GPC Biotech AG, 2005). In this dose finding study the maximum tolerated dose (MTD) of the combination of satraplatin and gemcitabine was evaluated. The hope was to subsequently explore the combination in a variety of solid tumors.

**PATIENTS AND METHODS**

**PATIENT SELECTION CRITERIA**

Eligibility criteria included histological diagnosis of metastatic or advanced-stage malignant solid tumors that had progressed following standard therapy or in whom no standard effective treatment was available. Subjects may have received up to two prior lines of chemotherapy for their metastatic disease. Patients with prior therapy with a platinum agent or gemcitabine were allowed as long as they obtained objective response to one of these agents and their disease occurred after 6 months. Other criteria included: age ≥18 years, ECOG performance status (PS) 0–2, adequate bone marrow function, adequate renal and hepatic function, measurable or non-measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST criteria v.1.0).

An independent ethical committee at San Camillo and Forlanini Hospitals approved the protocol. All patients signed written informed consent according to ICH Good Clinical Practice prior to study entry. The trial was conducted according to the Declaration of Helsinki and its amendments.

**TRIAL DESIGN AND PROCEDURES**

The study was conducted as a single-center, open label, dose escalation study combining gemcitabine with satraplatin in subjects with advanced solid tumors. Patients were stratified into two groups at registration according to the number of lines of prior chemotherapy (0 vs 1–2). Two separate MTDs were planned for patients with and without previous chemotherapy. The recommended phase II dose was defined as the same dose level as the MTD.

Initially, gemcitabine was given by IV infusion on days 1, 8, and 15 every 28 days followed by satraplatin p.o. for the first 5 days of each cycle (every 28-day schedule, part 1). Seventeen patients were enrolled and treated according to this 28-day schedule. Due to the increasingly common practice of giving gemcitabine and cisplatin on an every 3-week schedule and thrombocytopenia encountered with gemcitabine on the 28-day schedule, the protocol was subsequently amended to an every 21-day schedule (part 2). The second part of the study included 13 additional patients.

At screening and prior to each gemcitabine infusion, medical history, concomitant medication and PS were recorded. Adverse events were monitored throughout the trial. In both schedules patients were to receive up to 12 cycles. Treatment was discontinued after a dose delay of more than 3 weeks, need for more than one dose reduction, creatinine clearance below 40 ml/min, documented disease progression, or initiation of confounding anti-cancer therapy.

**DOSE ESCALATION**

The starting dose and dose escalation of gemcitabine and satraplatin in patients with prior chemotherapy and patients with no prior chemotherapy in parts 1 and 2 of the study are summarized in Tables 1 and 2. Dose escalations were planned in cohorts of three patients. If none of the three patients experienced a DLT during the first cycle, the next three patients were treated at a higher dose level. If any of the three patients experienced a DLT, three additional patients were treated at the same dose. If any of the six patients experienced

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**Table 1** | **Dose escalation in part 1 study (every 28-day schedule).**

| Dose level | Gemcitabine mg/m² days 1, 8, and 15* | Patients with prior chemotherapy | Patients with no prior chemotherapy |
|------------|-------------------------------------|--------------------------------|----------------------------------|
|            | Satraplatin mg/m²/day given daily for 5 days | Satraplatin mg/m²/day given daily for 5 days |
| Starting   | 800                                 | 40                             | 60                               |
| +1         | 1000                                | 40                             | 60                               |
| +2         | 1000                                | 60                             | 60                               |
| +3         | 1000                                | 80                             | 100                              |

*Cycles are to be repeated every 28 days.
Table 2: Dose escalation in part 2 study (every 21-day schedule).

| Dose level | Gemcitabine mg/m² days 1 and 8* | Patients with prior chemotherapy | Patients with no prior chemotherapy |
|------------|---------------------------------|----------------------------------|-----------------------------------|
| Starting   | 1000                            | 60                               | 80                                |
| +1         | 1000                            | 80                               | 100                               |
| +2         | 1000                            | 100                              | 120                               |
| +3         | 1250                            | 100                              | 120                               |

*Cycles are to be repeated every 21 days.

a DLT, the MTD was exceeded and three additional patients had to be treated at the lower dose (if only three patients were previously treated at that dose). The MTD was defined as the dose level at which 1/6 or 1/6 patients experience DLTs with the next higher dose having at least 2/3 or 2/6 patients experiencing a DLT.

Toxicities were graded on the basis of Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A DLT was defined as a drug-related CTCAE G3 or G4 non-hematologic toxicity (except reversible emesis or diarrhea) or G4 neutropenia of more than 7 days and/or complicated by infection or G3–G4 thrombocytopenia or any bleeding episode requiring platelet transfusion, or delayed recovery (to G1 or baseline, except alopecia). A toxicity related to the combination treatment which delayed initiation of the next cycle by more than 2 weeks was also a DLT.

TREATMENT, MTD, AND DLTs

The median number of cycles administered was 3. Five patients completed a total of 12 treatment courses, the maximum number of cycles per protocol. Details are reported in Table 4.

Every 28-day schedule part I of the trial

The trial was initiated with a 28-day schedule. The starting dose of satraplatin was 40 mg/m² in pretreated and 60 mg/m² in chemotherapy naïve patients (equivalent to 40 and 60% of the MTD of single-agent satraplatin).

In the “previous chemotherapy” group, three patients were treated at the starting dose (gemcitabine 800 mg/m² days 1, 8, and 15 plus satraplatin 40 mg/m² days 1–5; every 28 days). A DLT (G3 transaminases) was observed and the cohort was expanded to three more patients. Another DLT (G3 transaminases) was observed in this cohort. Thus, no patients were treated at the next dose level.

In the “no previous chemotherapy” group, eight patients were treated at the starting dose (gemcitabine 800 mg/m² days 1, 8, and 15 plus satraplatin 60 mg/m² days 1–5; every 28 days). Two patients were not evaluable for the MTD and were replaced. Both patients did not receive treatment on days 8 and 15 of cycle 1, due to G3 thrombocytopenia or withdrawal of consent during cycle 1. One DLT (G3 diarrhea) was observed in one of the six evaluable patients. Therefore, three additional patients received +1 dose level (gemcitabine 1000 mg/m² days 1, 8, and 15 plus satraplatin 60 mg/m² days 1–5; every 28 days). At dose level +1, one DLT (G3 thrombocytopenia) was observed in one of three patients. The starting dose (level 0) was therefore determined as the MTD.

In the “previous chemotherapy” group, no MTD was determined, and in the “no previous chemotherapy” group, the MTD was determined at dose level 0. Only 6 of 17 patients received gemcitabine on D8 and D15. Therefore, the protocol was amended in both groups to a more convenient every 3-week schedule.

Every 21-day schedule part II of the trial

In the “previous chemotherapy” group, seven patients were treated at the starting dose (gemcitabine 1000 mg/m² days 1 and 8 plus satraplatin 60 mg/m² days 1–3; every 21 days). One patient was not evaluable for the MTD, as he received no treatment on day 8 due to urinary infection. One DLT (G3 thrombocytopenia) was observed in one of six evaluable patients.
In the next three patients, the dose was escalated to dose level +1 (gemcitabine 1000 mg/m² days 1 and 8 plus satraplatin 80 mg/m² days 1–3; every 21 days). Two DLTs were observed (G3 thrombocytopenia).

The starting dose (level 0) was, therefore, determined as the MTD and further enrolment of six patients was planned. This was stopped after the first patient exhibited a DLT (G3 thrombocytopenia) due to a decision of the sponsor.

In the “no previous chemotherapy” group, two patients were treated at the starting dose (gemcitabine 1000 mg/m² days 1 and 8 plus satraplatin 80 mg/m² days 1–3; every 21 days). In each patient, one DLT was observed (G3 neutropenia and G3 thrombocytopenia). Dose level 0 was closed and the MTD could not be determined.

**Safety results**

All 30 patients received at least one dose of study treatment. A total of 137 cycles were evaluated for safety and 310 non-serious adverse drug reactions (ADRs) were recorded. Eighteen patients experienced 30 SAEs including 22 that were considered “possibly related” to study treatment. The reported serious ADRs were: diarrhea (1), rectal hemorrhage (1), ALT increase (3), low hemoglobin (4), low...
Table 4 | Treatment (cycles administered).

| N. of cycles administered | All patients | Part 1 | Part 2 |
|---------------------------|-------------|-------|-------|
|                           | No previous chemotherapy | Previous chemotherapy | No previous chemotherapy | Previous chemotherapy |
| Total                     | 137         | 38    | 25    | 4     | 70     |
| Median                    | 3           | 2     | 2     | 2     | 6      |
| Range                     | 1–12        | 1–12  | 2–12  | 1–3   | 2–12   |
| 12 cycles                 | 5           | 1     | 1     | 0     | 3      |

Platelets (8), neutropenia (2), elevated bilirubin (1), and deep venous thrombosis (1). G4 toxicities occurred in seven patients (three neutropenia, two anemia, one thrombocytopenia, and one pain). The predominant adverse event that occurred in greater than 20% of the patients are reported in Table 5. No major differences in adverse events G3–G4 were observed between the subjects in the two groups with and without prior chemotherapy.

**Table 5 | Adverse events in ≥20% of patients.**

| Adverse events | N. of patients with G1 | N. of patients with G2 | N. of patients with G3 | N. of patients with G4 | % of patients with (G1–G4) |
|----------------|------------------------|------------------------|------------------------|------------------------|---------------------------|
| Asthenia       | 6                      | 12                     | 4                      | 0                      | 73                        |
| Nausea         | 8                      | 7                      | 1                      | 0                      | 53                        |
| Thrombocytopenia| 3                      | 4                      | 7                      | 1                      | 50                        |
| Neutropenia    | 1                      | 3                      | 7                      | 3                      | 47                        |
| Anorexia       | 5                      | 8                      | 1                      | 0                      | 47                        |
| Anemia         | 0                      | 8                      | 2                      | 2                      | 40                        |
| Fever          | 7                      | 4                      | 0                      | 0                      | 37                        |
| Diarrhea       | 3                      | 4                      | 2                      | 0                      | 30                        |
| Constipation   | 9                      | 0                      | 0                      | 0                      | 30                        |
| Pain           | 5                      | 1                      | 0                      | 1                      | 23                        |
| Edema          | 5                      | 1                      | 0                      | 0                      | 20                        |

**DISCUSSION**

The purpose of this study was to determine the MTD and DLT of gemcitabine in combination with satraplatin in two groups of patients with advanced solid tumors. Since there was strong evidence of synergism of the combination of the two drugs in preclinical studies, it was decided to conduct the study in two groups of patients simultaneously.

The first group included patients previously treated with one or two lines of chemotherapy and for whom no further standard treatment was available. The second group included patients not previously treated with chemotherapy and for whom no further standard treatment was available. The second group included patients not previously treated with chemotherapy and for whom there was no standard treatment. This group included patients with pancreatic, gastric, hepatocellular carcinoma, biliary tract, or papillary renal cell cancers (Table 3). According to the protocol, more patients on the 28-day schedule at dose level 0 should have been included in order to verify if this was the recommended dose for phase II trials. However, taking into account the encouraging evidence of activity of the combination of the two drugs, as evidenced by a CR in a patient with pancreatic cancer, one PR in a patient with CRPC and one unconfirmed PR in a patient with biliary tract cancer, and the
fact that only 6 of 17 patients had received gemcitabine on days 8 and 15, the protocol was amended in both groups to a more feasible schedule (gemcitabine days 1 and 8, plus satraplatin days 1–3, every 21 days).

Unfortunately, the second part of the amended study was stopped after the FDA ODAC meeting in which satraplatin and prednisone in the SPARC trial failed to reveal an OS advantage in patients with CRPC and one prior line of chemotherapy. At that time only 30% of patients in the SPARC trial had received prior first-line treatment with docetaxel which was becoming the standard first-line chemotherapy.

The main objective of the study was to explore the safety of the combination of gemcitabine with satraplatin. For this reason, measurable disease was not required in the study. Of particular interest was the activity in patients with metastatic CRPC. The cycle length of 21 days would have provided a practical schedule. In addition, the efficacy of platinum-based treatment in prostate cancer has been noted. An oral platinum compound would have potentially been a very efficacious alternative to other chemotherapeutic agents (Oh et al., 2007). There were 13 CRPC patients enrolled, all of them were included after treatment with docetaxel and prednisone, and four also received a prior second line of chemotherapy.

Only seven CRPC patients had target lesions and were evaluable according to the protocol, while six were not evaluable for objective response. Four were not evaluable due to lack of measurable target lesions, one received less than two cycles and one was not re-evaluated. In this subgroup of evaluable patients with measurable lesions, the objective RR was 43%. Although the number of evaluable patients was limited due to study closure, the combination was feasible and patients were able to receive the maximum number of cycles permitted by the protocol (12 cycles).

In conclusion, the results of this study and the compliance with an oral platinum agent support the further development of satraplatin to better quantify its activity and safety in patients with CRPC after receiving docetaxel and other novel therapies such as abiraterone or enzalutamide. The combination was also interesting in pancreatic and biliary tumors.

ACKNOWLEDGMENT

This study was supported by GPC Biotech Inc., Princeton, NJ, USA.

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It is unfortunate that development of satraplatin was halted as it showed potentially interesting results in this study and other studies in ovarian cancer, lung cancer and as a radioenhancer for external beam radiation therapy. In actuality, satraplatin is under development as a radioenhancer and translational research studies with biomarkers are supported through a Material Cooperative Research and Development Agreement (MCRADA) with the NIH.

CONCLUSION

The arsenal of novel hormonal treatment for patients with CRPC has radically changed in recent years. Nonetheless, the results of this trial showed that the combination of gemcitabine and satraplatin, in particular given in an every 3 week cycle is feasible and has potential anti-tumor activity.

The results were encouraging, in particular, as second and third line chemotherapy in patients with CRPC, supported by the high objective RR of 43%. While the drug combination may be of interest in CRPC, the study did not prospectively enrolled a defined cohort of CRPC patients. Although the number of evaluable patients was limited due to study closure, the combination was feasible and patients were able to receive the maximum number of cycles permitted by the protocol (12 cycles).

In conclusion, the results of this study and the compliance with an oral platinum agent support the further development of satraplatin to better quantify its activity and safety in patients with CRPC after receiving docetaxel and other novel therapies such as abiraterone or enzalutamide. The combination was also interesting in pancreatic and biliary tumors.
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