Current Status and Future Prospects for Satraplatin, an Oral Platinum Analogue

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Abstract Platinum drugs are major chemotherapeutic agents that are used alone or in combination with other systemic agents and/or radiation therapy in the management of many human malignancies. All three platinum drugs approved by the Food and Drug Administration, cisplatin, carboplatin, and oxaliplatin, are administrated intravenously. Satraplatin is the first orally administered platinum drug under active clinical investigation. Satraplatin and its major metabolite, JM118, have shown antineoplastic activity in *in vitro, in vivo*, and in clinical settings. Use of satraplatin as an alternative platinum cytotoxic agent is particularly attractive because of the convenience of administration, milder toxicity profile, lack of cross-resistance with cisplatin, theoretical advantage as a radiosensitizer, and activity in cancers historically nonresponsive to platinum drugs. The most mature clinical data for satraplatin come from the recently completed phase III trial that investigated the efficacy of satraplatin and prednisone on hormone-refractory prostate cancer patients who had failed a course of other chemotherapy agents. Preliminary reports show that the combination is statistically superior to placebo and prednisone in multiple end points, including progression-free survival, prostate-specific antigen response, objective tumor response, pain response, and duration of pain response. The difference in overall survival, however, did not reach statistical significance.

Platinum drugs form a cornerstone of modern chemotherapy regimens for a variety of malignancies in both definitive and palliative settings. Cisplatin, first synthesized in 1847 and recognized for its antineoplastic activity since the 1960s, remains the platinum drug with the most proven efficacy. Carboplatin, with its milder side effect profile, is preferred by many clinicians as a substitute platinum drug because its activity is nearly comparable to cisplatin. Oxaliplatin is a new platinum drug that is used frequently for advanced gastrointestinal malignancies, previously thought to be unresponsive to platinum drugs. Taken together, these three drugs represent all of the available platinum drugs approved by the Food and Drug Administration (FDA) for clinical use. All three compounds, however, require i.v. administration. In some patients, platinum drugs can also induce anaphylactic or anaphylactoid reactions. Furthermore, *de novo* or acquired resistance to cisplatin is frequently observed, necessitating a change in treatment regimen. A new generation of platinum drugs, including satraplatin, is being developed by the pharmacologic research community to address these issues.

Although the overwhelming majority of chemotherapeutic agents are administered intravenously, a few oral anticancer agents such as capecitabine and erlotinib have been introduced into routine clinical practice in the last decade. These oral agents have been tested in a number of large clinical trials and were found to have efficacy comparable to those of intravenously agents. Oral chemotherapeutic agents offer the advantages of greater convenience, ease of administration, reduced need for office visits, and elimination of the need for venous access devices and their associated complications and costs. This review summarizes the pharmacologic properties and available clinical trials on satraplatin, the first orally bioavailable platinum derivative under active clinical investigation.

Other exciting new strategies of cytotoxic and biological systemic therapies are discussed elsewhere in this issue of *CCR Focus* (1–5).

Chemistry and Mode of Action

Satraplatin [*bis*-(acetato)-ammine dichloro-(cyclohexylamine) platinum(IV), JM216] was rationally designed for its desired properties (Fig. 1). The two axial acetate groups make the compound more lipophilic and increase its oral bioavailability. Once in blood, satraplatin is metabolized to lose its acetate groups to be structurally similar to cisplatin except for replacement of one of the amine groups with a cyclohexylamine group (6, 7). This metabolite, JM 118 *cis*-ammine dichloro (cyclohexylamine) platinum (II), in a similar fashion as does cisplatin, binds to DNA to form intrastrand and interstrand cross-links between adjacent purine bases (8, 9). These adducts distort the DNA template and inhibit DNA replication and transcription, which leads to cell cycle arrest in the G_2 phase and subsequent induction of apoptosis (8, 10).

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During their reaction with DNA, dichloro groups of platinum drugs are displaced (hence "leaving groups"), but the amine groups (or variations thereof) remain intact. These remaining moieties that determine the properties of the DNA binding are often called the stable ligands. Compared with platinum drugs approved by the FDA, satraplatin is unique in that its stable ligands are asymmetrical [an amine and a cyclohexamine, compared with the two amine groups of cisplatin or the (symmetrical) diaminecyclohexamine group of carboplatin], which contributes to its unique properties.

The DNA damage inflicted by satraplatin is repaired by a mammalian nucleotide excision repair pathway, with similar kinetics to the repair of damage by cisplatin and oxaliplatin (11). In contrast to cisplatin and carboplatin, however, satraplatin-induced adducts are not recognized by DNA mismatch repair proteins (12). In addition, some reports suggest that satraplatin-induced adducts, compared with adducts formed by other platinum drugs, do not bind to high mobility group 1 protein, which recognizes DNA damage caused by cisplatin and inhibits trans-lesion replication by certain DNA polymerases (13). These differences may provide a mechanism by which some platinum resistance may be overcome by satraplatin (14).

Preclinical Antineoplastic Activity

In vitro studies have shown antineoplastic activity of satraplatin and its active metabolites against several human cancer cell lines, including prostate (15, 16), ovarian (8, 16–18), cervical (19, 20), and lung (16, 21) cancers. In two independent experiments using the National Cancer Institute antitumor drug screen panel representing leukemia, small cell lung cancer, non–small cell lung cancer (NSCLC), central nervous system tumors, melanoma, colon, renal, and ovarian cancer cell lines, incubation with satraplatin for 48 hours induced growth inhibition of all 52 tested tumor cell lines in the first experiment and all 58 tested tumor cell lines in the second experiment (16).

Cytotoxicity data obtained in a panel of human ovarian cancer cell lines showed that IC_{50} values for satraplatin were comparable with those of cisplatin (8). In a panel of 10 cisplatin-sensitive small cell lung cancer cell lines, satraplatin was between 2- and 7-fold more potent than cisplatin (21). Satraplatin also showed activity against hormone refractory prostate cancer (HRPC) cell lines, with JM118 up to 16 times more potent than its parent drug, satraplatin, against prostate cancer cell lines (15, 16). Satraplatin also showed activity against selected cisplatin-resistant (16–18, 20, 21) and taxane-resistant (22) cell lines.

In vivo studies have tested the antineoplastic activity of satraplatin against a variety of tumor models. Satraplatin activity has been shown against murine plasmacytoma (17, 23), prostate cancer (23), ovarian cancer (17, 23), and colon cancer (23).

Satraplatin has been tested in combination with other cytotoxic agents. *In vitro*, satraplatin (or JM118) has shown additive or synergistic activity when combined with docetaxel (24), paclitaxel (24, 25), 5-fluorouracil (25), capecitabine (26), erlotinib (25, 27), oral etoposide (28), and trastuzumab (29).

Satraplatin was also tested in combination with radiation therapy. Mice implanted with H460 human lung cancer xenografts were given 30 mg/kg satraplatin orally and/or irradiated with a radiation dose of 2 Gy 1 hour later for 5 consecutive days (30). An additive effect was observed with the combination of satraplatin and radiotherapy, providing a rationale for exploring the clinical activity of concurrent chemoradiation therapy.

Clinical Trials

Phase I clinical trials: pharmacokinetics and toxicity. Satraraplatin is readily absorbed through gastrointestinal mucosa and undergoes rapid, complex biotransformation to yield at least six platinum-containing compounds, including its most active metabolite, JM 118 (31–34).

In the initial phase I trial, satraplatin was administered at doses ranging from 60 to 700 mg/m^2 as a single oral dose (33). The peak concentration (C_{max}) and area under the curve (AUC) of plasma platinum increased proportionally with doses up to 120 mg/m^2; however, at higher doses, C_{max} and AUC increased less in proportion to the dose administered, suggesting that the gastrointestinal absorption was being saturated. The maximum tolerated dose was never reached in this study. This prompted investigators to evaluate daily administration in a subsequent phase I pharmacokinetic study, in which satraplatin was given at doses from 30 to 140 mg/m^2/d for 5 days (34). Although there was a large interpatient

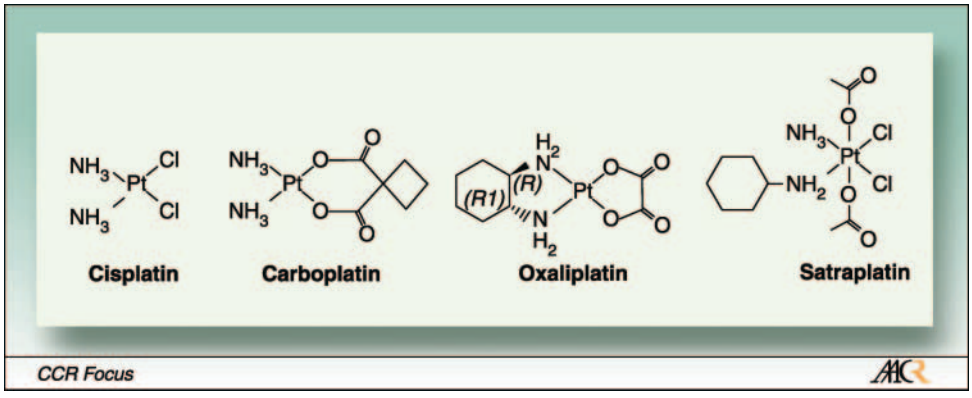

Fig. 1. Molecular structures of satraplatin and FDA-approved platinum drugs.

Table 1. Clinical efficacy of satraplatin monotherapy

Study	Histology	Dose, mg/m^2/d	*n*	Objective response rates, % (95% CI)
Latif et al. (CA142-013; ref. 50)	HRPC	120 orally on days 1-5, every 28 day	32	31 (13-42)
Sternberg et al. (EORTC 30972; ref. 51)	HRPC	100 orally on days 1-5, every 35 d + prednisone 10 mg orally twice daily	27	33 (17-54)
		Prednisone 10 mg orally twice daily	23	9 (1-28)
SPARC (53)	HRPC	80 orally on days 1-5, every 35 d + prednisone 5 mg orally twice daily	Total: 950	31% reduction of PFS event; 33% reduction of pain progression; 25% PSA response; 7% objective tumor response; 24% pain response
		Prednisone 5 mg orally twice daily		12% PSA response; 1% objective tumor response; 14% pain response
Judson et al. (56)	NSCLC	120 on days 1-5, every 3 wk	13	0 (0-21)
Fokkema et al. (57)	NSCLC	120 on days 1-5, every 3 wk	25	4 (0.001-0.2)
		Cisplatin 100 i.v. every 3 wk	23	13 (0.03-0.34)
Fokkema et al. (55)	SCLC	120-140 orally on days 1-5, every 3 wk	26	38 (19-58)
CA142-006 (58)	Recurrent ovarian cancer	100 orally on days 1-5, every 4 wk	20	35 (0.15-59)
		Cisplatin 100 i.v. every 4 wk or carboplatin 300 i.v. every 4 wk	20	35 (0.15-59)
Trudeau et al. (59)	Recurrent cervical cancer	30 orally on days 1-14, every 5 wk	18	6 (0.1-27.2)

Abbreviations: 95% CI, 95% confidence interval; PFS, progression-free survival; SCLC, small cell lung cancer.

variability, linear relationships were found between satraplatin dose and day 1 and day 5 ultrafiltrate platinum AUCs. The dose-limiting toxicities were thrombocytopenia and neutropenia, which were reversible and noncumulative. The most common grade 3 to 4 toxicities were gastrointestinal, including nausea, vomiting, and diarrhea, each occurring in ~10% of the patients. Nausea and vomiting were managed well by prophylactic use of serotonin blockers. Additional trials investigated daily oral administration of satraplatin for 5 days (35) or 14 days (36, 37). Again, the serum ultrafiltrate platinum AUC was linearly proportional to the daily oral administration dose.

Beale et al. (38) explored an alternative dose schedule of twice-daily doses given 12 hours apart. When doses ranging from 150 to 300 mg/m^2 were given twice daily to 19 patients, nonlinear pharmacokinetics was observed with no relationship between dose and AUC or C_{max}, suggesting that repeated daily dosing is superior.

Based on these trials of satraplatin as a single agent, a single oral dose or twice-daily dosing was felt to be unreliable. Recommended doses for phase II/III trials were 100 to 120 mg/m^2/d for 5 days (34, 35) or 45 to 50 mg/m^2/d for 14 days (36, 37). The predominant dose-limiting toxicities were hematologic and gastrointestinal, with a notable absence of high-grade nephrotoxicity (34–37, 39).

Phase I trials of satraplatin in combination with oral uracil-tegafur (UTF; ref. 40), i.v. paclitaxel (41), or radiotherapy (42–44) have also been conducted. A recently completed multi-institutional phase I trial of concurrent thoracic radiotherapy and daily satraplatin (5 days a week for 7 days) for locally advanced NSCLC showed dose-limiting toxicity (myelosuppression) at 40 mg/d when combined with a total radiation dose of 63 Gy. In the subsequent phase II trial, 30 mg/d of satraplatin will be given with high-dose (74 Gy) radiotherapy.[1]

Phase II and III trials: efficacy. Multiple phase II and III trials have been conducted to assess the efficacy and toxicity of satraplatin, alone or in combination with other cytotoxic therapies, for the treatment of various cancers (Table 1).

Prostate cancer. Until recently, HRPC has been widely considered resistant to chemotherapy, including cisplatin and carboplatin (46), although these studies were limited by traditional measures of radiographic response for treatment assessment (47). Two recent landmark trials, however, showed that docetaxel-based chemotherapy afforded statistically significant improvements in overall survival, prostate-specific antigen (PSA) response, pain relief, and quality of life, setting a new standard of care for HRPC patients (48, 49).

Satraplatin, either alone or with prednisone, showed promising antineoplastic activity in HRPC in a number of phase II and III clinical trials (50, 51). Latif et al. (50) reported the results of a phase II study (CA142-013) in which 39 HRPC patients were given satraplatin 120 mg/m^2/d for 5 days every 4 weeks. Of 32 patients with available PSA values, 10 (31%) had

[1] H. Choy, unpublished results.

either a complete or partial PSA response, 14 (44%) had stable disease, and 8 (25%) experienced PSA progression. Partial tumor responses were documented in 2 of 20 patients with measurable disease. Frequent dose delays (77%) and dose reductions (31%) occurred due to myelosuppression. Thus, the initial plan to repeat cycles every 21 days was changed to 28 days.

A phase III study conducted by European Organization for Research and Treatment of Cancer (EORTC 30972; ref. 51) sought to assess the role of satraplatin in chemotherapy-naive HRPC patients. Patients were randomized to receive either satraplatin 100 mg/m^2/d for 5 days every 5 weeks with prednisone 10 mg twice daily or prednisone alone. The trial was originally designed to accrue 380 patients, but it was prematurely terminated by the sponsor after 50 patients. Despite the small sample size, the trial showed that the satraplatin/prednisone combination increased progression-free survival (5.2 versus 2.5 months; $P = 0.023$), PSA response (>50% PSA decrease; 33.3% versus 8.7%; odds ratio 95% confidence interval, 1.00-2.78), and overall survival (14.9 versus 11.9 months, not statistically significant). The therapies were well tolerated in both arms.

Based on these promising findings, a large phase III trial was conducted to compare satraplatin plus prednisone versus placebo plus prednisone in HRPC patients who failed prior chemotherapy (52, 53). This Satraplatin and Prednisone against Refractory Cancer (SPARC) trial was similar to the EORTC trial in design, except that the patients were eligible if they had failed a course of cytotoxic chemotherapy. A total of 950 patients were accrued and randomized 2:1 to satraplatin (80 mg/m^2/d for 5 days every 5 weeks) and prednisone (5 mg twice daily) versus placebo and prednisone at the same dosage. Although 100 to 120 mg/m^2/d was initially recommended for phase II and III trials, the previously mentioned phase II study (CA142-01350) had shown that this dose schedule was associated with febrile neutropenia and extreme thrombocytopenia, requiring frequent dose delays and reductions. Therefore, the SPARC trial adopted the reduced dose of 80 mg/m^2/d for this previously heavily treated elderly population.

The preliminary results of the SPARC trial were first reported in February 2007 at the American Society of Clinical Oncology (ASCO) Prostate Cancer Symposium (52) and subsequently updated in the 2007 ASCO annual meeting (53). The satraplatin and prednisone arm was associated with fewer composite progression-free survival events (hazard ratio, 0.69; $P < 0.00001$), reduced risk of pain progression (hazard ratio, 0.67; $P = 0.00028$), superior PSA response (25% versus 12%; $P = 0.00007$), increased objective tumor response (7% versus 1%; $P < 0.002$), superior pain response (24% versus 14%; $P < 0.005$), and longer duration of pain response (hazard ratio, 0.59; $P = 0.049$). The primary end point, composite progression-free survival, was composed of radiologic progression, symptomatic progression, skeletal events, and death.

A recent analysis of overall survival showed, however, that there was not a statistically significant difference. The median overall survival for the satraplatin arm was 61.3 weeks, compared with 61.4 weeks for the control group ($P = 0.80$, log-rank analysis). Prespecified subset analyses are undergoing to identify if a subset of patients may have survival benefit (54).

Small cell lung cancer. In a phase II study, single agent satraplatin (120-140 mg/m^2/d for 5 days, repeated every 3 weeks) was given to 27 chemotherapy-naive patients with limited-stage (unfit for intensive chemotherapy) or extensive-stage small cell lung cancer (55). Of 26 patients available for tumor response assessment, 10 (38%) had achieved a partial response without any complete responses. These response rates are comparable with those observed with carboplatin. The median overall time to progression was 110 days and the median overall survival was 210 days. Grade 3 to 4 neutropenia, lymphocytopenia, and thrombocytopenia were, respectively, 19.6%, 64.7%, and 29.8%. No nephrotoxicity or neurotoxicity was seen.

NSCLC. Satraplatin monotherapy has shown little activity for advanced NSCLC. In one study, satraplatin 120 mg/m^2/d for 5 days, every 3 weeks, achieved no objective responses in 13 patients (56). When satraplatin monotherapy was compared with cisplatin monotherapy, a partial response was seen in 4% of the patients in the satraplatin arm and in 13% of the patients in the cisplatin arm (57).

When satraplatin was combined with radiotherapy for NSCLC, however, the outcomes were more favorable. In one phase I study conducted at Vanderbilt University, satraplatin 10 to 30 mg was administered thrice per week 1 hour before radiation therapy (60 Gy in 30 fractions). One complete response and six partial responses were observed in 15 NSCLC patients (42). This study provided the starting point for the phase I dose escalation trial that recently completed accrual in which radiation therapy (63 Gy at 1.8 Gy/fraction) and escalating doses of satraplatin (from 10 to 50 mg/d) were concurrently administrated for the duration of radiation therapy course.[2] At the conclusion of the satraplatin dose escalation study, additional patients will be evaluated with concurrent satraplatin (30 mg/d) with a higher dose of radiation therapy (74 Gy).[2]

Other tumor types. In the previously mentioned phase I study from Vanderbilt University, seven of eight patients with squamous cell carcinoma of the head and neck, who were treated with 10 to 30 mg of satraplatin thrice a week concurrently with radiotherapy (70 Gy; ref. 42), achieved a complete response.

Satraplatin showed similar efficacy as cisplatin and carboplatin in a phase II randomized trial of patients with recurrent ovarian cancer. In this study, satraplatin, given at a dose 100 mg/m^2/d for 5 days, was compared with standard doses of either cisplatin or carboplatin, depending on prior therapy. The objective response rates were 35% in both arms (58). A phase II study in patients with advanced or recurrent squamous cell carcinoma of the uterine cervix was reported (59). In this study, satraplatin was administered at a dose of 30 mg/m^2/d for 14 days, every 5 weeks. Of 18 patients, there was 1 partial response and 12 patients had a stable disease.

[2] Choy H., personal communications; 2007.

Expert Opinion

The FDA approval of oxaliplatin in 2004 for use in colorectal cancer represented the first change of scenery in the use of platinum drugs in over a decade. Until then, the field of platinum drug development seemed to have hit a wall with waning interests. With development of new, rationally designed platinum products, spearheaded by satraplatin (and shortly followed by picoplatin, another platinum designed to overcome cross-resistance by having a sterically hindered stable group), the platinum drugs promise to have a resurgence to the forefront of cancer therapy. The slow clinical development of satraplatin since its first clinical trials almost 15 years ago can be attributed to multiple factors such as its complex properties (e.g., nonlinear absorption, pharmacokinetics, and metabolism) and strategic decisions made by the pharmaceutical industry (e.g., focusing its attention on developing biological agents).

Currently, a recent phase III trial (SPARC) has met its accrual goal and preliminary results are very promising, with statistically and clinically significant improvements in progression-free survival, pain response, and PSA response. A recent analysis, however, did not show significant difference in overall survival. This may be due to several reasons including insufficient power of the study and difficulty delineating the exact causes of death. Subgroup analyses are now under way and cause-specific survival may need to be analyzed. Nevertheless, given that satraplatin is generally well tolerated, it may be used in a palliation setting to control symptoms and to delay progression.

Because satraplatin shares similar mechanism as cisplatin, it is reasonable to focus future development on those malignancies in whose management cisplatin has established roles, in combination either with other chemotherapeutic agents, especially oral agents, or with radiotherapy.

Combinations of satraplatin and other chemotherapeutic agents are being studied for synergistic or additive effects. For example, the combination of satraplatin with docetaxel as a first-line therapy in HRPC can be tested in a phase III study. Particularly attractive is the strategy of using an all-oral chemotherapeutic combination by combining satraplatin with capecitabine, oral etoposide, erlotinib, as well as future oral agents (e.g., oral taxane BMS-275183). A phase I study with a combination of satraplatin and capecitabine is currently open for patients with advanced solid malignancies. A phase II study with a combination of satraplatin and erlotinib is currently recruiting elderly patients with unresectable stage III/IV NSCLC.

It has been shown that cisplatin is more radiosensitizing when administrated on a daily basis during the course of radiation therapy (60). Several studies have been reported with low daily doses of cisplatin or carboplatin in combination with radiotherapy in the treatment of lung cancer, esophageal cancer, and head and neck squamous cell carcinoma (61–64).

Results of preclinical and clinical trials are promising in its use as a radiosensitizer in NSCLC as well as in head and neck squamous cell carcinoma (42). As previously mentioned, a phase I/II study of concurrent satraplatin and radiotherapy for locally advanced NSCLC has completed accrual of the dose-finding phase. The second phase, in which satraplatin (30 mg/d) will be administered throughout the duration of high-dose radiotherapy (74 Gy), is being planned.[2] Future phase II trials with this regimen might be conducted in head and neck squamous cell carcinoma and other malignancies in which the role of platinum drug as a radiosensitizer has been firmly established. In addition, a phase I trial of satraplatin plus radiation therapy to the prostatic bed is being planned for prostate cancer patients with biochemical failure after radical prostatectomy.

Conclusions

Satraplatin is the first orally administered platinum analogue that offers multiple potential advantages over the commonly used i.v. platinum drugs such as cisplatin. Its oral bioavailability makes it uniquely convenient both for patients and care providers. It seems to be comparable in efficacy to more established platinum drugs in multiple common human malignancies in preclinical experiments and in clinical trials. *In vitro*, it has shown activity against cancer cell lines that are resistant to cisplatin and may offer an attractive option for salvage chemotherapy. Satraplatin is similar in toxicity profile to carboplatin, with no nephrotoxicity, neurotoxicity, or ototoxicity observed. Moreover, it is much better tolerated than cisplatin and does not require hydration for each dose. There is now maturing clinical data of satraplatin in the second-line treatment of HRPC. If approved, satraplatin will offer many new possible strategies for cancer therapy.

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