Phase II Study of Liposomal Cisplatin (SPI-77) in Platinum-sensitive Recurrences of Ovarian Cancer

N. SEETHARAMU[1], E. KIM[1], H. HOCHSTER[1], F. MARTIN[2] and F. MUGGIA[1]

[1]*New York University School of Medicine, New York, NY 10016, U.S.A.;*
[2]*ALZA Pharmaceuticals, Inc., Mountain View, CA 94039-7210, U.S.A.*

Abstract. *Background: Cisplatin is a highly effective chemotherapeutic agent against epithelial ovarian cancer but is associated with significant toxicities. SPI-77 is a liposomal pegylated formulation of cisplatin that was developed to reduce systemic toxicity and to better deliver cisplatin to tumors. We assessed the response rates and safety of SPI-77, in patients with recurrent epithelial ovarian cancer. Patients and Methods: Patients were selected for having previously achieved a platinum treatment free interval of greater than 6 months (e.g. platinum-sensitive) and high potential of achieving responses when rechallenged with a platinum drug. SPI-77 was administered at a dose of 260 mg/m^2 every 21 days until disease progression. Results: Enrollment was terminated after 5 patients were treated because of concern with the adequacy of the formulation. Four out of the five patients had stable disease as best response. While no serious, unexpected adverse events occurred in spite of large cumulative doses of SPI-77, there were concerns related to the large lipid load and prolonged persistence of residual platinum in body stores. Conclusion: The results of this study, although inconclusive regarding its primary endpoints, provide some important lessons for the development of similar liposomal platinum agents.*

Cisplatin has had a major impact in the treatment of ovarian cancer but its use is often limited by gastrointestinal intolerance, nephrotoxicity, ototoxicity, peripheral neuropathy, and also, not infrequently, prolonged myelosuppression (1-4). Liposomal encapsulation of cisplatin was developed to deliver cisplatin to tumors with increased selectivity while decreasing the exposure of cisplatin to normal tissue. Such drug delivery is based on three pharmacological principles: i) a delay in drug bioavailability, thus slowing the release of the drug as well as reducing the peak level of free drug; ii) the relative bulkiness of lipid vesicles hindering extravasation of drug in tissues with a tight endothelium and continuous basement membrane such as in muscle and nervous tissue; and iii) 'passive targeting' of liposomes to tumor tissue by what has been called 'enhanced permeability and retention effect'. Its basis is the increased microvascular permeability inherent in many tumors coupled with poor lymphatic drainage resulting in high intratumoral concentrations compared to normal tissue (5, 6). SPI-77 is cisplatin encapsulated in long-circulating pegylated (Stealth®) liposomes. These Stealth liposomes are coated with methoxy-polyethylene glycol (MPEG) which makes them resistant to recognition by blood opsonins and renders them less susceptible to removal by the reticulo-endothelial system, resulting in dramatic changes in pharmacology in comparison to 'free' drug or classical liposomes (7, 8).

The pharmacokinetics of SPI-77 indicate that total platinum decays linearly with minimal interpatient variability, and total body clearance is significantly lower compared to 'free' cisplatin. Platinum (Pt)-DNA adduct levels in white blood cells ranged from 0.02 to 4.13 fmol/μg DNA for intrastrand Pt-GG (guanine-guanine) adducts and from 0.02-1.27 fmol/μg DNA for intrastrand Pt-AG (adenosine-guanine) adducts. These levels were more than ten fold lower than after administration of a comparable dose of free cisplatin (9).

Phase I studies of SPI-77 began in 1995 at doses ranging from 40 to 420 mg/m^2 (9). Side-effects included mild gastrointestinal toxicity (nausea and vomiting), and mild anemia, muscle weakness (at doses of ≥320 mg/m^2) and a case of infusion-related reaction. Serum cholesterol levels in patients were highly variable but increased with higher doses presumably related to a proportionally larger amount of lipid delivered. This safety profile was confirmed in phase II studies (10) and in the unpublished expanded part of the phase I study conducted at the University of Chicago and initially reported as an abstract (11). The current phase II study was to enroll patients with recurrent ovarian cancer with a progression free-interval of more than 6 months after

Correspondence to: F. Muggia, New York University School of Medicine, Bellevue C and D Building, Room 556, 462 First Avenue, New York, N.Y. 10016, U.S.A. Tel: +1 2122636485, Fax: +1 2122638210, e-mail: muggif01@med.nyu.edu

Key Words: Liposomal cisplatin, ovarian cancer, CA125.

Table I. *Demographics*.

Patient	Age (years)	Pathology, stage at dx	PFI (m)	Disease burden at start of SPI-77 treatment	Prior regimens	Baseline CA125 u/ml
A	48	Poorly differentiated, IIIC	22	2 cm supraclavcular LN, focal uptake of FDG in left neck, right lower lung, T4/T5 and presacral region.	1. Cyclophosphamide, carboplatin AUC 5×6 cycles 2. IP etoposide, IP Carboplatin AUC 3×3, & IP cisplatin 60 mg/m^2 added cycle 3; IP cisplatin 60 mg/m^2 ×1 cycle 3. Doxil 4. Carboplatin AUC 3, cisplatin 30 mg/m^2 ×5 cycles	21
B	44	Papillary serous, IIIC	23	Subhepatic lesions, cystic metastasis in the sigmoid mesocolon and in the left upper quadrant on CT.	1. Topotecan and cisplatin 75 mg/m^2 ×1 cycle 2. Paclitaxel and carboplatin AUC 6×6 cycles 3. IP FUDR and IP cisplatin 60 mg/m^2 ×3 cycles	58
C	39	Papillary serous, IIIB	41	Multiple hepatic lesions, perihepatic and pelvic fluid on CT.	1. Cyclophosphamide and cisplatin 75 mg/m^2 ×6 cycles 2. Paclitaxel and cisplatin 75 mg/m^2 ×4 cycles 3. Autologous bone marrow transplant (etoposide, paclitaxel, carboplatin)	296
D	63	Endometrioid adenocarcinoma, IC	41	1.8 cm peri-sigmoid implant on MRI & left supraclavicular lesion on PET.	1. Paclitaxel and carboplatin AUC 7-7.5 ×6 cycles 2. Tamoxifen 3. Doxil	248
E	62	Adenocarcinoma*, IIIx	26	Peritoneal carcinomatosis, pelvic floor disease, ascites, 1 cm implant hepatic dome on CT.	1. Paclitaxel and carboplatin AUC 5×6 cycles 2. Topotecan 3. Doxil and cisplatin 60 mg/m^2 ×8 cycles followed by Doxil maintenance	140

*Based on ascitic fluid. Staging laparotomy was done after initial chemotherapy regimen. PFI: Platinum-free interval; m, months.

their last platinum-based chemotherapy. It was initiated to test the hypothesis that SPI-77 would be active in a disease selected for sensitivity to platinum drugs. Because of interest in newer formulations of platinum compounds, the results of this study, even if closed early, may be relevant to future drug development. Therefore, the results of this small trial are presented in detail, and the perspective gained from other experience with SPI-77 is summarized.

Patients and Methods

Patients qualifying for study needed histologically or cytologically confirmed recurrence of epithelial ovarian cancer and a prior response with a platinum-free interval of at least 6 months. They were also required to have a Karnofsky performance status ≥70, an ANC ≥1500 cells/mL, platelet count ≥100,000 cells/ml, hemoglobin ≥9.0 g/dL, calculated creatinine clearance of ≥50 ml/minute, total bilirubin ≤2.0 mg/dL, AST ≤2 times the upper limits of normal, and an albumin ≥2.5 g/dL. Patients with ≥grade 2 pre-existing neuropathy were not eligible as were patients with a history of allergic reaction to cisplatin or platinum-containing products. The protocol was approved by the NYU Institutional Review Board, and patients provided signed informed consent.

Patients received 260 mg/m^2 of SPI-77 on day 1 of every 21-day cycle, and repeated until disease progression or serious adverse effects. The drug was administered IV in 1 liter volume of 5% dextrose over at least four hours. Premedication consisted of a corticosteroid, a H1-receptor antagonist and a H2-receptor antagonist (usually dexamethasone, granisetron, and diphenhydramine, respectively).

Physical examination and blood studies including CA125 serum level were obtained at baseline and on every cycle, and radiologic imaging (CT, MRI, or PET) at baseline and every 3 cycles to assess response. A complete response (CR) was defined as the disappearance of all gross evidence of disease. A partial response (PR) was defined by WHO criteria (12) as a 50% or greater reduction in the product obtained from measurement of each lesion and no evidence of disease progression on imaging. A CR or PR was confirmed at least four weeks later. Disease progression was defined as a 50% or greater increase in the product of any lesion, or the appearance of a new lesion. Stable disease was any condition not meeting the above criteria. If the CA125 was initially elevated, normalization of the marker must have occurred before a patient was considered to be in a complete clinical response. A rising CA125 by itself did not prompt classification of progression. NCI Toxicity Criteria (version 2.0) were used to grade adverse events.

Results

Enrollment into this study was conducted between April 1999 to February 2000, with entry of 5 platinum-sensitive patients with recurrent ovarian cancer. The patient characteristics and the prior treatments of the five patients who received SPI-77 are shown in Table I. All patients had

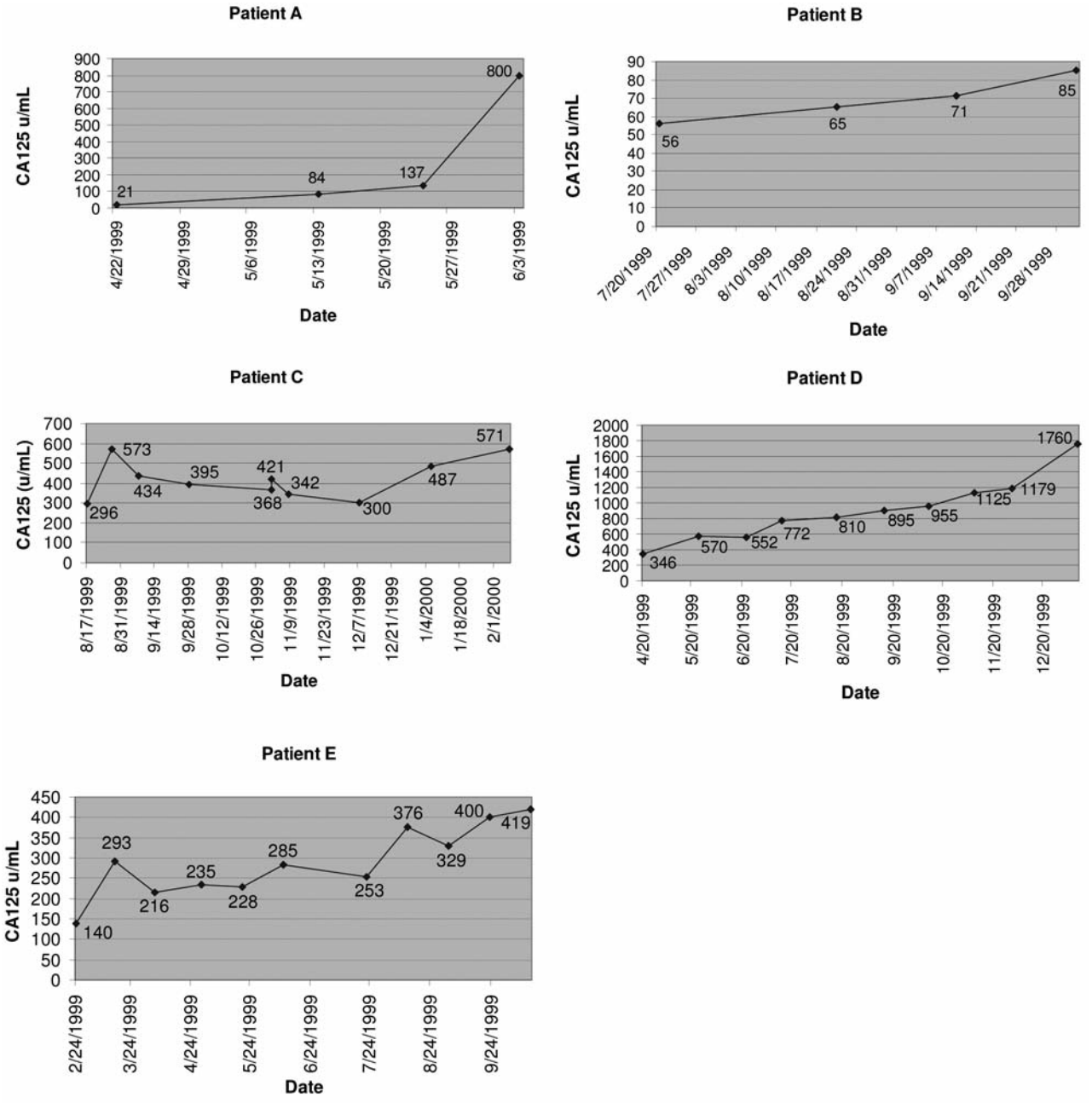

Figure 1. *CA125 values during SPI-77 therapy.*

received 3 to 5 prior chemotherapeutic regimens prior to receiving SPI-77 (Table I). The platinum free-interval ranged from 22 to 41 months.

Antitumor effects. Table II summarizes response and duration of response during SPI-77 therapy. In addition to no documented CR or PR on imaging, CA125 values during SPI-77 therapy were charted for the five patients and are shown in Figure 1. Patient A developed disease progression in the right chest and pleura having shown a PR in a supraclavicular node during the initial 8 weeks. She subsequently achieved a PR with carboplatin + gemcitabine. Patient B received four cycles of therapy while the CA125 continued to rise, and later CT scans showed obvious disease progression. She was later treated with carboplatin with no response. Patient C had a mixed response on CT with a decrease in size and number of hepatic metastases and interval resolution of perihepatic fluid, while new peritoneal implants along the greater curvature of

Table II. *Best response achieved*

Patient	No. of cycles of SPI-77	Response (Duration)
A	2	Stable disease (8 weeks)
B	4	No response
C	8	Mixed response* and categorized as stable disease (29 weeks)
D	10	Stable disease (37 weeks)
E	12	Stable disease (36 weeks)

*Decrease in size and number of liver metastases but at the same time development of new peritoneal lesions.

Table III. *Major adverse events and number of cycles of SPI-77 given.*

Patient	Adverse events	No. of cycles (cumulative dose)
A	Grade I anemia.	2 (520 mg/m^2)
B	Isolated febrile episode. Grade I nausea, vomiting.	4 (1040 mg/m^2)
C	Grade II nausea, vomiting. Grade I diarrhea.	8 (2080 mg/m^2)
D	None.	10 (2600 mg/m^2)
E	Grade II constitutional (fatigue). Grade I anemia.	12 (3120 mg/m^2)

Table IV. *Dyslipidemia from SPI-77**.

Cholesterol levels prior to SPI-77	Cholesterol levels during SPI-77
Median: 282.00 mg/dL Range: 193-357 mg/dL	Median: 433.67 mg/dL Range: 243-674 mg/dL

*Cholesterol values were available for three patients.

the stomach and probable splenic metastases were noted. CT scan after 8 cycles of therapy showed progressive metastatic disease in the liver as well as the development of multiple new omental and peritoneal metastases. Patient D had minimal disease on imaging by PET and MRI. Repeat CT scans and MRI abdomen failed to show evidence of disease progression even after ten cycles of SPI-77. The patient's CA125 continued to trend upward (Figure 1) and therapy was discontinued after a marked rise in the CA125 level (1179 to 1760 u/mL). Patient E maintained a relatively stable CA125 during SPI-77 therapy (Figure 1) and serial imaging with CT scans showed stable disease. After receiving 12 cycles of therapy, the patient presented with worsening ascites prompting insertion of a "pigtail" catheter for large volume paracentesis. Safety profile: Table III lists adverse effects that occurred during therapy and the number of cycles of SPI-77 given to each patient. No serious, unexpected adverse events occurred while receiving 2, 4, 8, 10, and 12 doses. No significant marrow suppression, renal insufficiency or liver function abnormalities developed. Table IV shows cholesterol levels in three patients before and during SPI-77 therapy. The median and range of cholesterol levels did appear to increase during SPI-77 therapy. No deaths occurred during SPI-77 therapy. Patients C and D were hospitalized with episodes of sepsis upon the first introduction of topotecan treatment at progression. Patient E died of liver and cardiac failure ("idiopathic" cardiomyopathy) of unknown etiology approximately one year after her last treatment of SPI-77. On autopsy, tissue platinum levels were assessed and were elevated, raising the possibility that her therapy with SPI-77 may have contributed to her demise.

Discussion

The liposomal formulation of cisplatin, SPI-77, was developed in order to increase selectivity of cisplatin to tumor sites and avoid systemic toxicity associated with 'free' cisplatin. Phase I studies demonstrated the ability to deliver ten-fold the amount of cisplatin per dose without encountering any toxicities beyond grade 1. However, few indications of therapeutic activity were encountered during the initial studies. Encouraged by the preclinical data and prior experience with the pegylated liposomes encapsulating doxorubicin, however, the sponsor was eager to obtain phase I-II data in a platinum-sensitive population. Therefore, studies in non-small cell cancer, and head and neck cancers, were carried out but were disappointing (see below). Accordingly, in this phase II trial on patients with potentially platinum-sensitive, relapsed ovarian cancer was to provide the ultimate test seeking for activity of this liposomal formulation.

We were able to assess a total of 36 cycles in the 5 patients entered. Some transient anti-tumor activity was noted: decrease in size and number of liver metastases in one patient and a decrease in size of a supraclavicular lymph node in another patient. Overall, 4 patients were classified as having stable disease, in 3 for periods exceeding 5 months (21 weeks). However, the CA125 continued to rise in all patients. On the other hand, despite large cumulative doses administered, SPI-77 did not demonstrate any of the platinum-associated dose-limiting toxicities, *e.g.* debilitating neuropathy, renal toxicity, neutropenia, that can occur with 'free' cisplatin. One cannot exclude the fact that long-term deleterious effects from the delivery of large amounts of lipid, and the deposition of platinum in the tissues, could have had a negative impact on the subsequent course of these patients.

Other clinical trials with SPI-77 also demonstrated minimal toxicity and lack of clinical response (10, 13-15). SPI-77 has also been studied in combination with other chemotherapeutic agents and external beam radiation (16,

17). While the toxicity profile in these studies was also found to be favorable, the drug did not seem to add to the efficacy of the regimen.

Lessons learned from these experiences may be applicable and relevant to subsequent liposomal formulations of cisplatin. Other liposomal and non-liposomal formulations have recently been studied in clinical trials. Several of these studies have demonstrated minimal platinum-associated toxicities (18-21). While this may be advantageous, such findings in a clinical study, including ours, would also be concerning for sub-optimal delivery of the cytotoxic platinum moiety to tissues and tumor. Another less well-defined concern would be prolonged persistence of platinum in storage pools which could result in delayed toxicities.

Acknowledgements

The Authors thank Dr. L. Juden Reed of the Albert Einstein College of Medicine, Bronx, NY 10461, U.S.A., and Dr. Leonard Seigel, M.D. of Holy Cross Hospital, Fort Lauderdale, FL 33308, U.S.A., for their helpful follow-up of patients C and D during and after treatment. This study was supported in part by the former Sequus Pharmaceuticals. T32 grant CA009454-21 supported Dr. Seetharamu.

References

1 Arany I and Safirstein RL: Cisplatin nephrotoxicity. Semin Nephrol *23*: 460-464, 2003.

2 Boulikas T and Vougiouka M: Recent clinical trials using cisplatin, carboplatin and their combination chemotherapy drugs (review). Oncol Rep *11*: 559-595, 2004.

3 McKeage MJ: Comparative adverse effect profiles of platinum drugs. Drug Saf *13*: 228-244, 1995.

4 Townsend DM, Deng M, Zhang L *et al*: Metabolism of cisplatin to a nephrotoxin in proximal tubule cells. J Am Soc Nephrol *14*: 1-10, 2003.

5 Samad A, Sultana Y and Aqil M: Liposomal drug delivery systems: an update review. Curr Drug Deliv *4*: 297-305, 2007.

6 Gabizon A: Tailoring liposomes for cancer drug delivery: from the bench to the clinic. Ann Biol Clin (Paris) *51*: 811-813, 1993.

7 Allen TM, Hansen C, Martin F *et al*: Liposomes containing synthetic lipid derivatives of poly(ethylene glycol) show prolonged circulation half-lives *in vivo*. Biochim Biophys Acta *1066*: 29-36, 1991.

8 Senior J, Delgado C, Fisher D *et al*: Influence of surface hydrophilicity of liposomes on their interaction with plasma protein and clearance from the circulation: studies with poly(ethylene glycol)-coated vesicles. Biochim Biophys Acta *1062*: 77-82, 1991.

9 Meerum Terwogt JM, Groenewegen G, Pluim D *et al*: Phase I and pharmacokinetic study of SPI-77, a liposomal encapsulated dosage form of cisplatin. Cancer Chemother Pharmacol *49*: 201-210, 2002.

10 Kim ES, Lu C, Khuri FR *et al*: A phase II study of STEALTH cisplatin (SPI-77) in patients with advanced non-small cell lung cancer. Lung Cancer *34*: 427-432, 2001.

11 DeMario MD, Vogelzang NJ and Janisch L: A phase I study of liposome-formulated cisplatin (SPI-77 R) given every 3 weeks in patients with advanced cancer). Proc Am Soc Clin Oncol 17, 1998.

12 Blessing JA: Design, analysis and interpretation of chemotherapy trials in gynecologic cancer. *In*: Chemotherapy of Gynecologic Cancer. Deppe G (ed.). New York: Alan Liss, Inc, pp. 68-72, 1984.

13 White SC, Lorigan P, Margison GP *et al*: Phase II study of SPI-77 (sterically stabilised liposomal cisplatin) in advanced non-small-cell lung cancer. Br J Cancer *95*: 822-828, 2006.

14 Veal GJ, Griffin MJ, Price E *et al*: A phase I study in paediatric patients to evaluate the safety and pharmacokinetics of SPI-77, a liposome encapsulated formulation of cisplatin. Br J Cancer *84*: 1029-1035, 2001.

15 Harrington KJ, Lewanski CR, Northcote AD *et al*: Phase I-II study of pegylated liposomal cisplatin (SPI-077) in patients with inoperable head and neck cancer. Ann Oncol *12*: 493-496, 2001.

16 Rosenthal DI, Yom SS, Liu L *et al*: A phase I study of SPI-077 (Stealth liposomal cisplatin) concurrent with radiation therapy for locally advanced head and neck cancer. Invest New Drugs *20*: 343-349, 2002.

17 Vokes EE, Gordon GS, Mauer AM *et al*: A phase I study of STEALTH cisplatin (SPI-77) and vinorelbine in patients with advanced non small-cell lung cancer. Clin Lung Cancer *2*: 128-132, 2000.

18 Ravaioli A, Papi M, Pasquini E *et al*: Lipoplatin monotherapy: A phase II trial of second-line treatment of metastatic non-small-cell lung cancer. J Chemother *21*: 86-90, 2009.

19 Stathopoulos GP, Boulikas T, Vougiouka M *et al*: Pharmacokinetics and adverse reactions of a new liposomal cisplatin (Lipoplatin): phase I study. Oncol Rep *13*: 589-595, 2005.

20 Hamelers IH and DeCroon AIPM: Nanocapsules of platinum-based anticander drugs. *In*: Platinum and Other Heavy Metal Compounds in Cancer Chemotherapy. Bonetti A, Leone R, Muggia F *et al*. (eds.). Humana Press, pp. 27-32, 2008.

21 Monte E, Gariboldi MB and Rivezza R: Assessment of the *in vivo* antiproliferative activity of a novel platinum particulate pharmacophore. *In*: Platinum and Other Heavy Metal Compounds in Cancer Chemotherapy. Bonetti A, Leone R, Muggia F *et al*. (eds.). Humana Press, pp. 19-26, 2008.

Received January 8, 2010
Accepted January 18, 2010