Phase I Clinical and Pharmacological Study of Liposome-entrapped cis-Bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane Platinum(II)

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ABSTRACT

cis-Bis-neodecanoato-trans-R,R-1,2-diaminocyclohexaneplatinum(II) (NDDP) is a liposome dependent cisplatin analogue since the liposome carrier is required for its i.v. administration and for its biological activity. A Phase I study of liposome entrapped NDDP (L-NDDP) was performed using a single i.v. injection every 4 weeks. L-NDDP was prepared and characterized at M. D. Anderson Cancer Center. The maximum tolerated dose of L-NDDP was 312.5 mg/m². The dose-limiting toxicity was myelosuppression, affecting all three blood cell lineages. The granulocyte nadir occurred on days 14–18, and the platelet nadir consistently earlier (days 11–12). The median day of recovery of blood cell counts was day 21 (range, 18–32). Other toxicities included grade 2 nausea and vomiting, fever consisting of a single temperature spike in most patients, grade 1 diarrhea after 60% of courses, and grade 1–2 malaise lasting for 5–10 days after the infusion in 73% of courses. Transient alanine aminotransferase elevations without clinical relevance were common. No signs of renal dysfunction or otoxicity were observed. One patient with a preexisting peripheral neuropathy showed some progression of the neuropathy after a cumulative dose of 1605 mg/m². Except for fever and transient liver dysfunction, no liposome related side effects were observed in spite of the high doses of lipid administered. The blood clearance of L-NDDP fits a two-compartment model at lower doses and a single-compartment model at the maximum tolerated dose, suggesting that saturation of the reticuloendothelial organs occurs at the maximum tolerated dose. Two minimal responses were observed. L-NDDP has a toxicity profile similar to that of carboplatin. Phase II studies to address the issue of how the therapeutic index of platinum compounds is affected by liposome entrapment are being planned.

INTRODUCTION

Liposomes are microscopic phospholipid vesicles that target naturally to organs that have fenestrated capillaries and are rich in phagocytes as the liver, spleen, and bone marrow (1–11). Entrapment of drugs in liposomes modifies their pharmacokinetics, organ distribution, and metabolism. The ability of liposomes to avoid certain organs provides a way to prevent organ specific toxicities such as doxorubicin cardiotoxicity (12). Several liposome anticancer products are currently being tested in humans (5–10).

Cisplatin is one of the most useful antitumor agents available (13, 14). Its main limiting toxicity is nephrotoxicity which can be prevented in most patients by intensive hydration prior to its administration. Cisplatin is not myelosuppressive, which allows for combination with myelotoxic agents. The use of cisplatin is currently limited by its limited spectrum of activity, its chronically induced neurotoxicity, and the emergence of resistance in originally sensitive tumors. Carboplatin is a second generation cisplatin derivative that is less nephrotoxic and neurotoxic but is myelosuppressive, mainly causing thrombocytopenia (15). Carboplatin has been recently approved by the Food and Drug Administration for commercialization based on its reduced nephrotoxicity and neurotoxicity. Because of its myelotoxic potential, carboplatin is currently being explored as an antileukemic agent with encouraging preliminary results (16). However, carboplatin has a similar spectrum of activity and is cross-resistant with cisplatin (17). The development of a cisplatin derivative with activity against cisplatin resistant tumors and reduced toxicity would represent a significant step forward.

cis-Diaminocyclohexane dichloroplatinum(II) is a cisplatin derivative with a cyclohexane ring attached to the amino groups and has been available for almost two decades. It has remarkable biological properties, such as reduced nephrotoxicity and a lack of cross-resistance in murine systems (18, 19). Unfortunately, it is completely insoluble in water and most organic solvents and, therefore, cannot be administered i.v. Water soluble derivatives of cis-diaminocyclohexane dichloroplatinum(II) have been previously developed and tested in humans (20–22). However, the studies were limited or not completed because of formulation problems. The potential use of this family of compounds in cisplatin resistant tumors was, therefore, never adequately tested.

In 1985, we started an in-house program aimed at developing lipophilic cis-diaminocyclohexane dichloroplatinum derivatives designed for liposome entrapment for the treatment of tumors that involve the organs of the reticuloendothelial system and/or are resistant to cisplatin. As a result, a liposomal formulation of one of these compounds (NDDP) was selected for further development. The preclinical toxicology and antitumor activity of L-NDDP have been published (23–25). Briefly, L-NDDP was found to be devoid of nephrotoxicity. The major toxicity in mice was myelosuppression and in dogs the lethal dose resulted in an acute and diffuse hemorrhagic syndrome involving mainly the gastrointestinal tract. L-NDDP was found to be active against tumor models resistant to cisplatin and more active than cisplatin against liver and spleen metastases of M5076 reticulosarcoma and RAW 117 H-10 lymphoma in mice. We report here the results of a Phase I clinical and pharmacological study of L-NDDP administered i.v. every 4 weeks.

MATERIALS AND METHODS

Synthesis and Characterization of NDDP

NDDP was synthesized in our laboratories at M. D. Anderson Cancer Center as reported previously in detail (23). All batches were characterized by elemental analysis, melting point, ¹⁹⁵Pt nuclear magnetic resonance, and IR spectroscopy. The chemical structure of NDDP is shown in Fig. 1.

1 The abbreviations used are: NDDP, cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexaneplatinum(II); L-NDDP, liposome entrapped NDDP; MTD, maximum tolerated dose.
PHASE I STUDY OF LIPOSOME ENTRAPPED NDDP

Preparation and Characterization of L-NDDP

L-NDDP was prepared in our laboratories as a lyophilized powder in bottles containing 100 mg of NDDP and 1500 mg of a mixture of phospholipids (dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol at a 7:3 molar ratio). Phospholipids were obtained from Avanti Polar Lipids (Birmingham, AL). In brief, chromatographically pure phospholipids were dissolved in chloroform, the solution was placed in a round bottomed flask, and the chloroform was evaporated in a rotary evaporator at 40°C in a sterile hood. The lipid film was then dissolved in tert-butyl alcohol (1 mg of NDDP/ml) to achieve a final lipid:NDDP weight ratio of 15:1, and aliquots of 100 ml of the solution containing NDDP and the phospholipids were placed in sterile bottles after filtration through a membrane filter of regenerated cellulose, pore size 0.22 μm (Micro Filtration Systems). The bottle contents were then frozen over dry ice and acetone and lyophilized for 24 h in a Labconco freeze-drier 8 (Labconco Corp., Kansas City, MO).

Prior to administration, L-NDDP was reconstituted by adding 100 ml of 0.9% sodium chloride in water solution to each bottle and shaking the suspension in a water bath shaker (Versa Bath, model 224; Fisher Scientific, Pittsburgh, PA) for two consecutive periods of 20 min at 24°C (at 80 rpm during the first period and at 120 rpm during the second period). This protocol was strictly used for all doses to ensure optimal reproducibility. At the completion of the reconstitution process, the bottle was manually shaken for 30 seconds to ensure proper dissolution of any remaining aggregates.

All lyophilized L-NDDP batches were characterized by physical appearance, phospholipid content and integrity, elemental platinum content, sterility, and pyrogenicity. Phospholipid content was assessed by determining the amount of phosphatidylglycerol at a 7:3 molar ratio). Phospholipids were obtained from Phospholipid Inc. (Piscataway, NJ). The phospholipid content was determined by the Bartlett assay. Lipid content, sterility, and pyrogenicity were assessed using the Limulus amebocyte lysate assay. Batches of lyophilized L-NDDP were considered acceptable if they met the following criteria: white flaky powder on physical appearance; lipid content between 85 and 115% of label claim, lipid impurities <3%, platinum criteria: white flaky powder on physical appearance, lipid content and integrity, elemental platinum was measured by X-ray fluorescence at the Department of Analytical Chemistry, University of Texas Health Sciences Center at Houston. Sterility was assessed according to Food and Drug Administration protocol 610.2 (Federal Register 38, 32056, 1973). Pyrogenicity was assessed by the L. dissimiled L-NDDP were considered acceptable if they met the following criteria: white flaky powder on physical appearance, lipid content between 85 and 115% of label claim, lipid impurities <3%, platinum content between 1 and 2%, no growth in any of the culture media, and endotoxin content <0.25 ng/mg NDDP.

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All reconstituted batches of L-NDDP were characterized by physical appearance, NDDP entrapment, and size profile. NDDP entrapment was assessed by the Limulus amebocyte lysate assay. Batches of lyophilized L-NDDP were considered acceptable if they met the following criteria: white flaky powder on physical appearance, lipid content between 85 and 115% of label claim, lipid impurities <3%, platinum content between 1 and 2%, no growth in any of the culture media, and endotoxin content <0.25 ng/mg NDDP.

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Study Design

Eligibility Criteria. Patients were entered into the study provided: they had histological proof of malignancy refractory to conventional forms of treatment, life expectancy >2 months, performance status <2 (Zubrod scale), measurable disease, age >18 years, adequate bone marrow function (granulocyte count >1,500/mm³, platelet count >100,000/mm³), adequate liver function (bilirubin <1.5 mg/100 ml), adequate renal function (creatinine <1.5 mg/100 ml); they were at least 18 years old; they had given written informed consent; and at least 3 weeks had elapsed since their previous therapy. Patients clinically resistant to cisplatin were eligible.

Treatment Plan. L-NDDP was given i.v. once every 4 weeks in the inpatient service. The rate of infusion was in all cases 4 mg NDDP/min. The starting dose was 7.5 mg NDDP/m² (lipid dose, 112.5 mg/m²) which corresponds to one-tenth of the mouse 10% lethal dose. Subsequent dose escalations were as follows: 15, 30, 45, 67.5, 100, 125, 160, 200, 250, 312.5, and 390 mg NDDP/m² (lipid dose, NDDP dose x 15). Dose escalation in the same patient was allowed if the toxicity observed was grade 2, nausea and vomiting excluded. All patients received 1 liter of 0.9% sodium chloride in water solution over 4 h and 25 g mannitol over 15 min just prior to the administration of L-NDDP, and 1 liter of 0.9% sodium chloride in water solution over 4 h after the completion of the infusion. Antinausea premedication with metoclopramide, 1 mg/kg, and diphenhydramine, 25 mg i.v. over 15 min, was given to most patients treated with doses higher than 45 mg NDDP/m². L-NDDP infusion was started between noon and 2 p.m. in all cases.

Patient Characteristics

Study Table 1 shows the characteristics of the patients entered in the study. A total of 39 patients (26 males and 13 females) received at least one dose of L-NDDP. Most patients had tumors that are considered to be naturally resistant to cisplatin. Eleven patients (28%) had tumors commonly treated with front line cisplatin containing regimens (4 non-small cell carcinoma
of the lung, 4 head and neck carcinoma, 2 germ cell tumors, 1 osteosarcoma). All these patients except one (with non-small cell carcinoma of the lung) had been treated previously with cisplatin and were clinically resistant to it.

A total of 107 doses of L-NDDP were administered. The median cumulative dose of L-NDDP given to any patient was 312.5 mg/m² (range, 22.5–1605 mg/m²). Two patients received a total cumulative dose >1,000 mg/m² (1560 and 1605 mg/m²). Seven patients received 1 dose each, 18 patients 2 doses, 4 patients 3 doses, 5 patients 4 doses, 1 patient 5 doses, 2 patients 6 doses, 1 patient 7 doses, and 1 patient 8 doses. Two patients received 2 doses at 390 mg/m², and 1 patient received 4 doses at 390 mg/m².

Side Effects

Table 2 shows the frequency and intensity of the different side effects observed at each dose level.

**Nausea and Vomiting.** The frequency and intensity of vomiting was clearly dose related up to a dose of 160 mg/m². At higher doses, most patients had grade 2 vomiting in spite of the premedication, but its intensity was not significantly increased. Vomiting generally started approximately 2 h after the completion of the infusion and lasted for 3–4 h with no further vomiting beyond 12 h of the completion of L-NDDP infusion. All patients were able to have breakfast the next morning.

**Diarrhea.** Diarrhea was observed at doses of 100 mg/m² and higher. The frequency and intensity of diarrhea were not clearly dose related. Diarrhea consisted of 2–3 liquid stools occurring 2–4 h after the completion of L-NDDP infusion, without cramps or other symptoms.

**Fever.** A single temperature spike (<39.5°C) occurred in most patients at doses of 100 mg/m² and higher 10–12 h after the completion of L-NDDP infusion. It was asymptomatic and did not require treatment in most instances. It was accompanied by chills in only one case. Fever duration was less than 4 h in all cases since it was never recorded in 2 consecutive 4-h-interval measurements. Fever intensity was not dose related and did not change significantly with subsequent treatments. Because of its lack of clinical relevance, no further studies were consistently performed to assess its cause in this study.

**Myelosuppression.** Myelosuppression was the dose limiting toxicity of L-NDDP. At doses higher than 200 mg/m², dose related anemia, granulocytopenia, and thrombocytopenia were observed.

At the highest dose administered, 390 mg/m², thrombocytopenia was observed after 10 of 15 courses (3 grade 1, 2 grade 2, 1 grade 3, and 4 grade 4), anemia was observed after 11 courses (6 grade 1, 3 grade 2, and 2 grade 3), and granulocytopenia was observed after 11 courses (1 grade 2, 5 grade 3, and 5 grade 4). Three patients treated at 390 mg/m² required platelet transfusions. No episodes of infection or hemorrhage associated with myelosuppression were observed.

The baseline values, median day of nadir values, and median nadir hemoglobin, platelet count, and granulocyte count observed at doses of 250, 312.5, and 390 mg/m² are shown in Table 3. The nadirs of the hemoglobin and granulocyte counts occurred at the end of the second week or beginning of the third week (day 15 at a dose of 390 mg/m²). The platelet nadir occurred consistently a few days earlier (day 11). In many cases platelet counts were found to start dropping as early as 3 days after L-NDDP infusion.

Six of 10 patients had grade 4 myelosuppression at a dose of 390 mg/m² in the form of granulocytopenia (2 patients), thrombocytopenia (2 patients), or both (2 patients). They all had previously received various chemotherapy regimens, including mitomycin C or 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea in 3 of them. The median duration of grade 4 myelosuppression (time to recover to values in a range corresponding to grade 3 or less) was 4 days (range, 3–4 days). The median day of recovery of myelosuppression in this subgroup of patients (first day of all values within normal range) was day 21.5 (range, 18–32).

Two of the three patients treated repeatedly with a dose of 390 mg/m² had significant myelosuppression. The severity of granulocytopenia and thrombocytopenia tended to increase with each additional dose of L-NDDP administered. In one patient treated with four consecutive doses of 390 mg/m², the granulocyte and platelet nadir values decreased from 670/mm³ and 80 x 10³/mm³, respectively, after the first dose, to 100/mm³ and 14 x 10³/mm³ after the fourth dose. This patient had been treated previously with 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea. In the other patient, who received two consecutive doses of L-NDDP at 390 mg/m², the nadirs were 1000/mm³ and 81 x 10³/mm³ after the first dose, and 400/mm³ and 107 x 10³/mm³ after the second dose.

**Malaise.** Malaise, consisting of tiredness and lack of energy, was observed with increased frequency and intensity at doses higher than 250 mg/m². At 390 mg/m², malaise was observed after 11 of 15 courses (5 grade 1 and 6 grade 2) (73%).

**Renal Dysfunction.** Creatinine elevations were not detected at any dose level.

**Liver Dysfunction.** Acute and transient elevations of alanine aminotransferase were observed after 11 of 15 courses at 390 mg/m² [median baseline value, 25 units/ml (range, 13–187); median peak value, 101 units/ml (range, 27–254)]. The alanine aminotransferase values peaked on days 3–6 and returned to baseline on days 12–14 in all cases. No increases in alkaline phosphatase or bilirubin that could be definitely attributed to L-NDDP were observed. Liver dysfunction abnormalities were not cumulative with subsequent courses of therapy in the same patient.

**Ototoxicity and Neurotoxicity.** No patient complained of...
hearing loss or tinnitus. Two patients complained of mild paresthesias in hands and feet after several doses of L-NDDP (cumulative L-NDDP doses, 542.5 and 1605 mg/m²). No electromyographic changes were detected in the first patient after a cumulative dose of 542.5 mg/m². The second patient's baseline electromyogram showed a mild motor neuropathy. A repeat electromyogram after a cumulative dose of 1605 mg/m² showed a mild to moderate motor and sensory neuropathy.

Other Toxicities. No acute respiratory problems related to the administration of L-NDDP were observed in spite of the high lipid dose administered. No allergic reactions were observed. No patient deaths occurred during the study.

Pharmacology Studies

Fig. 2 shows the elemental platinum clearance curves in patients treated with 200, 250, 312.5, and 390 mg/m² of L-NDDP. At the lower doses (200 and 250 mg/m²), drug clearance showed a relatively rapid initial distribution phase followed by a prolonged elimination phase. With increasing doses of L-NDDP, the initial distribution phase was more prolonged and drug clearance tended to be monophasic, fitting a one-compartment model. The calculated pharmacokinetics parameters are shown in Table 4. Although the number of patients studied was small, the following trends were observed. The $C_{p0}$ increased proportionately with the dose. At 390 mg/m², the mean $C_{p0}$ was 6.35 µg/ml, which is similar to that observed in dogs at the MTD (150 mg/m²). The $Vd_{0}$ was fairly constant, representing approximately 50% of body weight at all dose levels studied. Although the $t_{1/2}$ varied among patients particularly at the highest dose level, the elimination half-life ($t_{1/2}$) was fairly constant at all doses, ranging between 14 and 36 h. The $C \times t$ was markedly increased with increasing dose levels: at a dose of 200 mg/m², the mean $C \times t$ was 3,312 µg platinum/ml/min; at a dose slightly less than double, 390 mg/m², the mean $C \times t$ was 13,428 µg platinum/ml/min, i.e., approximately 4 times higher. At the highest dose level, 390 mg/m², two of the three patients studied (patients 1 and 2) had grade 4 myelosuppression while patient 3 did not present significant myelosuppression. Their $C \times t$ were 11, 404, 18,087, and 10,793 µg platinum/ml/min, respectively.

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**Table 2** L-NDDP phase I study: side effects

<table>
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<tr>
<th>Dose (mg/m²)</th>
<th>No. of courses</th>
<th>Nausea + vomiting</th>
<th>Diarrhea</th>
<th>Fever</th>
<th>Myelosuppression</th>
<th>Fatigue</th>
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<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>100</td>
<td>11</td>
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<tr>
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<tr>
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<td>3 (gr. I) 6 (gr. II)</td>
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<tr>
<td>250</td>
<td>8</td>
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<td>3 (gr. I) 8 (gr. II)</td>
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<tr>
<td>312.5</td>
<td>7</td>
<td>1 (gr. I)</td>
<td>3 (gr. I) 7 (gr. II)</td>
<td>Thrombocytopenia</td>
<td>1 (gr. I) 5 (gr. I)</td>
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<tr>
<td>390</td>
<td>15</td>
<td>2 (gr. I)</td>
<td>9 (gr. I) 14 (gr. II)</td>
<td>Thrombocytopenia</td>
<td>3 (gr. I) 5 (gr. I)</td>
<td></td>
</tr>
</tbody>
</table>

* gr., grade.

**Table 3** Myelosuppression secondary to L-NDDP therapy

<table>
<thead>
<tr>
<th>Dose level (mg/m²)</th>
<th>Hemoglobin (g/100 ml)</th>
<th>Granulocytes ($\times 10^9$/mm$^3$)</th>
<th>Platelets ($\times 10^9$/mm$^3$)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline (range)</td>
<td>Nadir (range)</td>
<td>Day (range)</td>
</tr>
<tr>
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<td>11.7 (10.3-13.6)</td>
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<tr>
<td>312.5</td>
<td>10.8 (8.9-13.0)</td>
<td>9.8 (7.8-10.9)</td>
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<td>390</td>
<td>11.7 (9.4-14.2)</td>
<td>10.2 (6.8-12.7)</td>
<td>13 (2.3-7.8)</td>
</tr>
</tbody>
</table>

Heating error.
Antitumor Activity

Thirty-three patients received two or more courses of L-NDDP and were evaluable for response. Nine patients remained stable, and 23 patients had disease progression after 2 courses of L-NDDP therapy. Evidence of antitumor activity was observed in two patients graded as stable. One had locally advanced breast carcinoma and had not been treated before with cisplatin. Serial ultrasound exams showed a measurable reduction in tumor size, but not to less than 50% of the product of the baseline perpendicular diameters. The second patient had renal cell carcinoma metastatic to the liver, spleen, and lungs and had been treated previously with cisplatin. After two courses of L-NDDP, the spleen lesion was no longer evident in the computed tomographic scan, while the liver and lung disease remained stable. This patient continued treatment with L-NDDP for several additional courses, until his disease progressed in the liver and lung, although not in the spleen.

DISCUSSION

This study shows that a liposome entrapped lipophilic cisplatin analogue (L-NDDP) can be administered safely to patients with metastatic tumors. The side effects of L-NDDP include acute nausea, vomiting, diarrhea, and fever and subacute myelosuppression. The MTD of L-NDDP was 312.5 mg/m². Myelosuppression was the dose-limiting toxicity.

Myelosuppression affected the three blood cell lineages and was of short duration (<5 days). The hemoglobin and granulocyte nadirs occurred on days 14–18, while the platelet nadir occurred consistently earlier, around day 12 in most cases. Platelet counts started to drop as early as 3 days after drug infusion. This phenomenon was observed even in patients treated with doses well below the MTD. Myelosuppression appeared to be cumulative with the administration of consecutive doses of L-NDDP.

The toxicity profiles of L-NDDP and cisplatin have in common only the gastrointestinal side effects. It is difficult from the results of the study to compare the intensity of vomiting secondary to L-NDDP and cisplatin. However, according to most patients previously treated with cisplatin, nausea and vomiting were less intense with L-NDDP than with cisplatin. L-NDDP is not nephrotoxic while kidney dysfunction is the limiting toxicity of cisplatin. However, L-NDDP is a myelosuppressive agent, while cisplatin generally is not. Longer term study of the neuro- and ototoxic potential of L-NDDP will be required before conclusions can be reached, since these are chronic toxicities. The toxicity profiles of L-NDDP and carboplatin are more similar than those of L-NDDP and cisplatin since both analogues are myelosuppressive and not nephrotoxic (15). However, carboplatin appears to predominantly cause thrombocytopenia while L-NDDP causes both granulocytopenia and thrombocytopenia.

The only side effects observed with L-NDDP that might be liposome related are fever, transient liver dysfunction, and malaise. The fever is probably secondary to macrophage activation and release of interleukin 1. It has also been reported with other liposome entrapped chemotherapeutic agents, such as liposomal doxorubicin (8–10). The transient liver dysfunction may be the result of the preferential partition of NDDP to the hepatocytes in the liver. Malaise may be related to liver dysfunction or macrophage activation (release of tumor necrosis factor). All these liposome related side effects were asymptomatic or well tolerated. These observations provide further evidence that high doses of liposomes can be safely administered i.v. to humans.

In preclinical studies, the lethal toxicities of L-NDDP were myelosuppression in mice and gastrointestinal toxicity in the form of necrotizing enterocolitis in dogs (23). The results of the current study indicate that the mouse model was more predictive of the dose limiting toxicity in humans than the dog. However, the dog model was predictive of other toxicities, such as nausea and vomiting and liver dysfunction.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose level (mg/m²)</th>
<th>Cₚₒ (µg Pt/ml)</th>
<th>Vₐ (ml/kg)</th>
<th>tₐ₀ (min)</th>
<th>tₐ₀ (h)</th>
<th>Cl (ml/kg/min)</th>
<th>C × t (µg Pt/ml/min)</th>
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<tr>
<td>1</td>
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Table 4 L-NDDP phase I study: pharmacokinetics parameters
The pharmacokinetics studies showed that the clearance of L-NDDP from the blood is dose related. At lower doses, the drug is cleared following a 2-compartment model with a rapid initial phase of drug distribution and a prolonged elimination phase. At higher doses (MTD), the drug is cleared following a single compartment model, with a half-life similar to the t½, seen at lower doses. The most likely explanation for this observation is that the initial distribution phase corresponds to rapid uptake of the liposome material by the liver, spleen, and bone marrow. With increasing doses of the material, the reticuloendothelial system becomes saturated, and the drug remains mainly in the intravascular compartment and is slowly cleared from the blood. The peak drug levels and C × t were the only parameters that were clearly dose related. However, the number of patients studied is too small to confirm a definite correlation between these parameters and the degree of myelosuppression. Two of the three patients studied at the highest dose (390 mg/m²) had grade 4 myelosuppression. Their C × t were 11,404 and 18,087 ng platinum/ml/min. A third patient did not have myelosuppression and his C × t was not significantly different, 10,793 μg platinum/ml/min. Since individual patients could not be studied at different dose levels, we cannot establish from the results of the current study a correlation between the degree of toxicity and the changes in clearance or C × t in individual patients. Phase II studies with L-NDDP are planned for the near future. In that context, we will attempt to correlate biological activity with the clearance of total blood, vesicle-bound, lipoprotein-bound, and free NDDP.

REFERENCES

Phase I Clinical and Pharmacological Study of Liposome-entrapped cis-Bis-neodecanoato-trans-R,R,-1,2-diaminocyclohexane Platinum(II)

Roman Perez-Soler, Gabriel Lopez-Berestein, Julio Lautersztain, et al.


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