Phase I Clinical and Pharmacological Study of Liposome-entrapped NDDP Administered Intrapleurally in Patients with Malignant Pleural Effusions

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ABSTRACT
cis-Bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum(II) (NDDP) is a lipophilic non-cross-resistant platinum compound formulated in large multilamellar liposomes (1–3 μm). The maximum tolerated dose (MTD) of liposomal-entrapped NDDP (L-NDDP) administered i.v. in humans is 300 mg/m², and myelosuppression is the dose-limiting toxicity. L-NDDP administered i.p. is absorbed slowly from the peritoneal cavity of rats. Recently, i.p. cisplatin has been shown to be superior to i.v. cisplatin in improving the survival of patients with ovarian carcinoma and minimal residual disease. We conducted a Phase I study to determine the MTD, side effects, kinetics of absorption into the systemic circulation, and preliminary antitumor activity of L-NDDP administered intrapleurally in patients with free-flowing malignant pleural effusions. Twenty-one patients were treated with escalating doses of L-NDDP by intrapleural administration over 30 min every 21 days. Fourteen patients had adenocarcinoma of the lung, 5 patients had malignant pleural mesothelioma (MPM), and 2 patients had ovarian carcinoma. The dose-limiting toxicity of L-NDDP was chest pain secondary to chemical pleuritis, which was severe in three of four patients treated at 550 mg/m². The MTD was 450 mg/m². At this dose, the only toxicity observed was grade 1-2 nausea and vomiting presenting 6–8 h after drug administration. Neither myelosuppression nor nephrotoxicity was observed. Localization of residual pleural fluid with continued decrease over a period of weeks to months was observed in seven patients; in one of these patients (MPM), the pleural effusion disappeared without evidence of recurrence for 19+ months, and in six patients (three adenocarcinoma of the lung, two MPM, and one ovarian carcinoma), the pleural effusion was reduced by >50% for 5+, 10+, 18+, 8, 5+, and 2+ months. Plasma pharmacokinetic studies showed that the absorption of L-NDDP from the pleural cavity was rapid during the first 2 h, with levels becoming steady (bioavailable or free platinum) or increasing slowly (total plasma platinum) between 6 and 24 h after administration. Urinary excretion was negligible (1–3%). We conclude that: (a) the MTD of Intrapleural L-NDDP is 50% higher than the MTD after i.v. administration; (b) intrapleural L-NDDP causes mild nausea and vomiting and no myelosuppression at the MTD; and (c) the absorption of L-NDDP into the systemic circulation is much slower than that of the parent compound cisplatin. Because of the favorable depot effect, lack of systemic toxicity, and control of the pleural effusion in three of five patients with MPM, a disease similar to ovarian carcinoma in that it tends to remain confined to a body cavity, a Phase II study of intrapleural L-NDDP administered in patients with MPM is in progress.

INTRODUCTION
Malignant pleural effusions are caused by diffuse obstruction of the visceral pleura lymphatics and capillaries by tumor tissue (1). Except in the case of MPM (2), which originates in the pleura, the presence of a malignant pleural effusion is a manifestation of distant metastatic spread from an extrathoracic malignancy or locally advanced disease in the case of lung cancer. The main clinical manifestations of a malignant pleural effusion are dyspnea due to compression of the underlying lung and pleuritic chest pain. Ideally, the treatment of a malignant pleural effusion should be the treatment of the primary disease. However, no effective treatment for the primary disease is available in many cases of symptomatic malignant pleural effusions. Thoracentesis alone is useful for temporary palliation, but recurrence of the effusion is the rule. Treatment aimed at preventing recurrence of the effusion, by administering into the pleural space substances such as tetracyclines or talc that promote the adherence of the visceral and parietal pleura (chemical pleurodesis), is effective in a very high proportion of patients (3). However, it requires hospitalization for chest tube placement to drain completely the effusion before the intrapleural

The abbreviations used are: MPM, malignant pleural mesothelioma; L-NDDP, liposomal cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum(II); AUC, area under the curve; OV, ovarian; AD, adenocarcinoma; MTD, maximum tolerated dose.
Intrapleural L-NDDP for the Treatment of Malignant Pleural Effusions

Figure 1: Chemical structure of NDDP. R1, R2, and R3 can be a 2–6 carbon group to yield a radical with C10H19O1 as its empirical formula (Mw 651,000).

instillation of tetracycline is performed. Insufflation with talc is probably even more effective.

Intrapleural administration of chemotherapy for the treatment of malignant pleural effusions has been explored previously. The purpose is to control the effusion as a result of a direct antitumor effect. Several studies on the intrapleural use of cisplatin and cytosome arabinoside, mitomycin C (4–6), etoposide (7), methotrexate and leucovorin (8), and bleomycin (9) have been reported. Most studies showed significant antitumor/pleurodesis efficacy, as determined by the lack of recurrence of the pleural effusion but not as high as with tetracycline. Drug levels measured concomitantly in pleural fluid and plasma provided documentation of the pharmacological advantage associated with the intrapleural administration of the drugs.

In the context of a study in which cisplatin and mitomycin C were given intrapleurally to patients with MPM after surgical resection (4), the pharmacokinetics of intrapleural cisplatin were studied and were found to be very similar to those of i.p. cisplatin (10). Cisplatin is absorbed quickly from both cavities; plasma levels peak at 15–20 min and are similar to those achieved with i.v. cisplatin. Therefore, and in spite of a markedly increased pleural AUC compared with plasma AUC after the intrapleural administration of cisplatin, cisplatin is not an ideal agent for intracavitary therapy.

L-NDDP is a lipophilic cisplatin analogue that has been formulated in multilamellar liposomes measuring from 1 to 3 μm in diameter (Refs. 11 and 12; see chemical structure in Fig. 1). In a Phase I study by i.v. administration, the maximum tolerated dose was 300 mg/m2, and the limiting toxicity was myelosuppression (12). Nausea and vomiting were mild, and no nephrotoxicity was observed. L-NDDP has been shown to be not cross-resistant with cisplatin in several in vitro and in vivo systems (12, 14–16). Several studies have demonstrated the favorable depot properties of liposomes after s.c. or intracavitary administration (17). In a Phase I-II study of liposomal doxorubicin by i.p. administration in patients with ovarian cancer (18), the drug was very well tolerated, with no systemic toxicity; the peritoneal fluid doxorubicin levels were about 50-fold higher than concurrent plasma levels, and 3 of 10 patients responded.

We previously studied the plasma and peritoneal fluid pharmacokinetics of rats treated with cisplatin and L-NDDP i.v. and i.p. (19). Absorption of L-NDDP from the peritoneal cavity was much slower than that of cisplatin (peak plasma levels at 12–24 h versus 20–30 min), and the peritoneal fluid levels of L-NDDP were severalfold higher than those of cisplatin at 6 h. These studies suggest that L-NDDP has a much more favorable pharmacokinetic profile for i.p. administration when compared with cisplatin.

Based on the broader spectrum of antitumor activity of L-NDDP, its potentially enhanced tumor penetration abilities because of its lipophilic nature (20) and its demonstrated delayed absorption from the peritoneal cavity in rats (19), we decided to study the toxicity, preliminary antitumor activity, and pharmacokinetics of L-NDDP after intrapleural administration in patients with malignant pleural effusions. We report here the results of this study.

PATIENTS AND METHODS

This study was conducted under IND 30,984 assigned to the University of Texas M. D. Anderson Cancer Center and was given prior approval by the Institutional Review Board.

Objectives. The objectives of the study were to determine the MTD, the clinical side effects, the plasma pharmacokinetics, and the preliminary antitumor activity of L-NDDP administered intrapleurally.

Patient Eligibility. To be eligible for the study, patients had to meet the following criteria: (a) cytologically proven, free-flowing malignant pleural effusion as the main site of primary or metastatic disease; (b) not eligible for other therapies shown to have an impact on survival; (c) no prior pleurodesis; (d) performance status on the Zubrod scale of ≤2 and life expectancy of ≥3 months; (e) no anticancer therapy during the 3 weeks prior to study entry; (f) no concomitant other anticancer therapy; (g) age ≥18; (h) adequate bone marrow (WBC count ≥4,000/mm3; absolute granulocyte count ≥1,500/mm3; and platelet count ≥100,000/mm3); kidney (creatinine ≤1.5 mg/dl) and liver (bilirubin ≤1.5 mg/dl; alanine aminotransferase ≤1.5 the upper limit of normal); (i) patients with brain metastases were eligible if asymptomatic or controlled with radiotherapy; and (j) no evidence of severe heart disease or intercurrent illness. All patients signed an informed consent before being enrolled in the study.

Prestudy Evaluation. Prestudy evaluation consisted of a complete history and physical examination; laboratory tests including blood counts, blood chemistry, and electrolytes; urinalysis; EKG; chest-X-ray; bone scan; and computed tomography scans of chest, abdomen, and brain to fully assess the extent of the pleural and extrapleural disease, and pleural fluid studies including cytology, cell count, lactate dehydrogenase, protein, and glucose.

Evaluation during Study. Blood counts, blood chemistries, and urinalysis were performed weekly for 4 weeks after the first course of L-NDDP and every 2 weeks after subsequent courses. Urinalysis and chest X-ray were performed before each course of L-NDDP. Pleural fluid studies were repeated with each intrapleural administration of L-NDDP.

Evaluation of Response. Appropriate radiographic studies to evaluate changes in the size of the pleural effusion were performed after the second course of therapy and/or every 3 months after the completion of therapy. In all cases, a chest X-ray performed after the infusion of L-NDDP was used as baseline.
Evaluation of Toxicity. The common National Cancer Institute toxicity criteria were used to assess the severity of nausea, vomiting, alopecia, fever, pain, and myelosuppression.

Preparation 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 (dimyristoyl phosphatidyl choline and dimyristoyl phosphatidyl glycerol at a 7:3 molar ratio), as described previously (13, 21).

Prior to administration, L-NDDP was reconstituted by adding 50 ml of 0.9% sodium chloride in water solution to each bottle as described (13). All lyophilized L-NDDP batches were characterized by physical appearance, phospholipid content and integrity, elemental platinum content, sterility, and pyrogenicity. All reconstituted batches of L-NDDP were characterized by physical appearance, NDDP entrapment, and size profile. Because the stability of lyophilized L-NDDP and reconstituted L-NDDP has not been fully elucidated, an expiration period of 48 h was established for all lyophilized L-NDDP batches, and all reconstituted L-NDDP doses were administered between 3 and 4 h after reconstitution.

Treatment Plan. L-NDDP was given intrapleurally via an intrapleural catheter every 3 weeks on an outpatient basis. The intrapleural catheter was placed immediately before the administration of L-NDDP and removed at the completion of the infusion. An amount of pleural fluid at least equal to the volume of L-NDDP suspension to be infused was drained. In all cases, significant fluid remained in the cavity. A chest X-ray was performed at the completion of the L-NDDP infusion and used as baseline for response assessment. The pleural fluid obtained was sent for studies as described above.

The starting dose of L-NDDP was 75 mg/m² (2250 mg/m² of lipid). Subsequent escalations were 150, 300, 375, 450, and 550 mg/m². Patients were eligible to receive additional courses of L-NDDP provided they continued to have a free-flowing pleural effusion and they had recovered from all toxicities. Patients with fluid loculation after one cycle were not eligible for a second cycle because of technical difficulties in repeating the thoracentesis. Dose escalation was permitted within patients provided that no biological activity other than nausea and vomiting was observed with the first dose. No premedication to prevent nausea and vomiting was given in any case.

Pharmacology Studies. Pharmacology studies were carried out in the four patients treated at the highest dose, 550 mg/m², because the intended plan was to start the studies at the dose level resulting in systemic biological activity. Blood samples (5 ml) were drawn in heparinized tubes at the completion of L-NDDP infusion and at 15 and 30 min, and 1, 2, 3, 4, 6, and 24 h after the completion of L-NDDP infusion and kept at 4°C. Sample collections at 48 and 72 h were also planned, but none of the patients studied returned for those time points. The plasma was obtained by centrifuging the blood samples at 2000 × g for 10 min at 4°C. A fraction of the plasma (0.2 ml) was dissolved in 0.8 ml of methanol and centrifuged for 2 min to collect the supernatant containing the methanol extractable plasma components. Another plasma fraction (0.8 ml) was used to obtain the plasma ultrafiltrate by using the Centrifree tubes and centrifuging at 2000 × g for 15 min at 4°C. Urine was collected during each 24-h period for up to 72 h after administration; then the volume was measured, and aliquots were stored. Elemental platinum levels in total plasma, methanol-extractable fraction of the plasma, plasma ultrafiltrate, and urine were determined by flameless atomic absorption spectrophotometry as described previously (18), expressed in μg/ml, and the pharmacokinetic parameters were calculated. The plasma C × t (AUC) was determined by the trapezoidal rule.

RESULTS

Patient Characteristics

A total of 25 patients was registered, of whom 21 received at least one dose of L-NDDP. The other four patients were never treated because of unsuccessful thoracentesis. All treated patients are evaluable for toxicity and changes in the size of the pleural effusion. The patient characteristics are shown in Table 1. Fourteen patients had AD of the lung (11 with stage III-B disease and 3 with stage IV disease), 5 patients had MPM, and 2 patients had OV carcinoma. Four patients had received prior chemotherapy, four patients had prior radiotherapy, and two patients received both.

A total of 28 doses of L-NDDP was given. Fourteen patients received one dose only, and seven patients received two doses. No patient received three doses. The number of cycles given at each dose level were as follows: 75 mg/m² for three cycles; 150 mg/m² for five cycles; 300 mg/m² for six cycles; 375 mg/m² for four cycles; 450 mg/m² for five cycles; and 550 mg/m² for four cycles. Three new patients were enrolled at each dose level were as follows: 75 mg/m² for three cycles; 150 mg/m² for five cycles; 300 mg/m² for six cycles; 375 mg/m² for four cycles; 450 mg/m² for five cycles; and 550 mg/m² for four cycles. Three new patients were enrolled at each dose level, except at 300, 450, and 550 mg/m², where four patients were entered. All patients who received two cycles received the second cycle at an escalated dose. These patients are distributed as follows: two patients entered at 75 mg/m²; two patients entered at 150 mg/m²; one patient entered at 300 mg/m²; and two patients entered at 375 mg/m². None of the eight patients entered at 450 and 550 mg/m² received a second cycle due to either rapid fluid reaccumulation deemed to be secondary to progressive disease (four patients) or fluid loculation (four patients).

Table 1 Patient characteristics

<table>
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<tr>
<th>Number</th>
<th>%</th>
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<td>4, 19</td>
</tr>
<tr>
<td>Chemotherapy + radiotherapy</td>
<td>2, 10</td>
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</table>
Intrapleural L-NDDP for the Treatment of Malignant Pleural Effusions

Changes in Size of Pleural Effusion

Changes in the size of the pleural effusion were assessed by using the chest X-ray performed after the infusion of L-NDDP as baseline. In one patient with MPM (4.7%), the pleural effusion disappeared completely. In six patients (two with MPM, three with AD of the lung, and one with OV carcinoma; 28.5%), the size of the pleural effusion decreased by >50%. In seven patients (two with MPM and five with AD of the lung; 33.2%), there was no change in the size of the pleural effusion, and in seven patients (six with AD of the lung and one with OV carcinoma; 33.2%), there was an increase in the size of the pleural effusion.

Fourteen patients received only one dose of L-NDDP, in 9 cases because of fluid loculation and in 5 cases because of fluid reaccumulation deemed to be secondary to disease progression. In the nine patients with fluid loculation after one cycle of L-NDDP, the amount of fluid was unchanged in five (one with MPM and four with AD of the lung) and was reduced by >50% in four (one with MPM, one with OV carcinoma, and two with AD of the lung). Reduction in the amount of fluid was not immediate and, in general, was progressive over a period of months. Initial fast fluid reaccumulation with negative cytology followed by progressive reduction over a period of 2 months was documented in one case of OV carcinoma.

Seven patients received 2 cycles of L-NDDP (two MPM and five AD). Fluid loculation was observed after the second dose in four patients (two MPM and two AD). In the other three, reaccumulation of cytologically positive pleural fluid was observed. Of the four patients with fluid loculation, in one patient with MPM the pleural effusion disappeared completely over a period of months; in two with AD, there was a >50% reduction, and in the other patient with MPM, there was no change.

Table 2 shows the changes in the size of the pleural effusion by number of courses, pleural fluid loculation, cumulative dose, and histology. Of the five patients with MPM, one had a complete disappearance of the pleural effusion and is alive and free of disease at 21+ months, 2 had a >50% reduction of 8 and 6+ months duration, and 2 had no change. Of these last 2, one died at 4 months with progressive disease, and the other was switched to systemic chemotherapy with cytoxan, Adriamycin, and cisplatin, with continued evidence of tumor shrinkage at 7+ months.

Only three patients with lung AD had measurable disease outside of the chest. None of these patients responded to therapy. No responses were seen either in the mediastinal disease of the three patients with stage III-B lung AD whose pleural effusion responded to the therapy.

Toxicity

The toxicities observed were limited to nausea and vomiting and chest pain secondary to chemical pleuritis (Table 3).

Gastrointestinal Toxicity. Nausea and vomiting were dose related. Grade ≥2 nausea and vomiting was observed after one of six cycles at 300 mg/m², two of four cycles at 375 mg/m², four of six cycles at 450 mg/m², and two of four cycles at 550 mg/m². Grade 3 was observed after one of four cycles at 550 mg/m².

Nausea and vomiting started characteristically 6–8 h after completion of L-NDDP infusion and lasted for about 12 h. It was controlled with oral antiemetics. In only 1 case, one of the patients treated at the highest dose of 550 mg/m², the treatment led to dehydration and required i.v. fluid administration. Diarrhea was not observed in any case, in contrast with the Phase I study by i.v. administration (13).

Chest Pain. Chest pain was only observed at the highest dose of 550 mg/m² and was severe in three of four patients, requiring oral narcotics in two cases and i.v. narcotics in one case. It was pleuritic in nature, associated with generalized tiredness and weakness, and lasted for several weeks. It was associated with rapid pleural fluid reaccumulation in all three cases. In two of them, the fluid reaccumulation was secondary to local chemical inflammation. One of these patients had MPM, is alive with only residual pleural thickening, and has not had fluid reaccumulation for 5 months.

Fever. Fever was only consistently observed (three of four patients) at the highest dose level of 550 mg/m². It occurred about 12 h after drug infusion and was limited to a single spike with no other clinical manifestations or consequences.

Myelosuppression. Myelosuppression was not observed at any dose level. This is the major difference with the toxicity observed after i.v. administration, where at the MTD of 300 mg/m², myelosuppression, mainly granulocytopenia, was the dose-limiting toxicity (13). This observation suggests a significant systemic protection to the effects of the drug by using the intrapleural route of administration.

Other Toxicities. As in the study by i.v. administration (8), no signs of kidney dysfunction or neurotoxicity, either peripheral neuropathy or ototoxicity, were observed.

Maximum Tolerated Dose

The highest safe dose of intrapleural L-NDDP was 450 mg/m². At this dose, which corresponds to the MTD, only grade 1–2 nausea and vomiting were observed without premedication. At the next higher dose, 550 mg/m², chest pain with fast pleural fluid reaccumulation secondary to chemical pleuritis, documented by pleural fluid cytology in one case, was observed in three of four patients. This dose is, therefore, considered to be above the MTD. The recommended dose and schedule for Phase II studies is 450 mg/m² every 3 weeks.

<table>
<thead>
<tr>
<th>Cumulative dose (mg/m²)</th>
<th>Pleural fluid</th>
<th>No. of patients</th>
</tr>
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<tr>
<td></td>
<td>Loculation</td>
<td>Disappearance</td>
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<tr>
<td>75</td>
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<td>1 (AD)</td>
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<tr>
<td>150</td>
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<td>1</td>
</tr>
<tr>
<td>225</td>
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<td>1 (AD)</td>
</tr>
<tr>
<td>300</td>
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<td>375</td>
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<td>1 (AD)</td>
</tr>
<tr>
<td>450</td>
<td>1</td>
<td>1 (MPM)</td>
</tr>
<tr>
<td>550</td>
<td>3</td>
<td>2 (MPM,OV)</td>
</tr>
<tr>
<td>675</td>
<td>1</td>
<td>(MPM)</td>
</tr>
<tr>
<td>825</td>
<td>2</td>
<td>1 (AD)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>13 (61.9)</td>
<td>1 (4.8)</td>
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</table>
**Pharmacokinetics**

Plasma platinum levels could only be determined in four patients treated at the highest dose of 550 mg/m² within the first 24 h after therapy. Peak plasma levels were observed in all four patients at 24 h (later time point samples were not obtained) and ranged from 0.92 to 2.8 µg/ml (Table 4). The absorption of NDDP into the systemic circulation was biphasic, with an initial phase of rapid absorption lasting for 2 h, followed by a phase of slow but continuous increase in plasma levels lasting up to the last time point determined (24 h). The plasma levels at 24 h were 3-4-fold lower than the peak plasma levels obtained after the i.v. administration of a dose of 390 mg/m² of L-NDDP over a period of 4 h, as reported previously (13). Fig. 2 shows the plasma levels of total platinum, methanol-extractable platinum, and ultrafilterable platinum in the four patients studied.

Ultrafilterable and methanol-extractable platinum represent noncovalently bound, bioavailable NDDP. The curves of plasma levels of methanol-extractable platinum and ultrafilterable platinum were similar to those of total plasma platinum, although they tended to plateau earlier, after 6 h. As a result, the percentage of platinum accountable in both fractions at 24 h was about one-half of that at 6 h (methanol-extractable platinum, 19.2% at 24 h versus 46.3% at 6 h; ultrafilterable platinum, 11.7% at 24 h versus 20% at 6 h; Table 5). The onset of nausea and vomiting at 6 h coincides, therefore, with the time that bioavailable NDDP peaks in plasma.

The 24-h $C \times t$ (AUC) was calculated from the start of drug infusion to 24 h after administration, and ranged between 12 and 40 µg/ml/h for plasma total platinum, which is about 18- and 5-fold lower, respectively, than the 24-h $C \times t$ observed with an i.v. dose of L-NDDP of 390 mg/m² (Table 4). The 24-h $C \times t$ for ultrafilterable and methanol-extractable platinum was 2–6 and 2–14 µg/ml/h, respectively. Intrapleural administration, therefore, confers a significant systemic protection, thus explaining the lack of myelosuppression, which is the dose-limiting toxicity of i.v. L-NDDP (13).

Pleural fluid levels were not measured because the intrapleural catheter was removed in all cases after the completion of L-NDDP infusion. The urinary excretion was measured in three patients and ranged between 0.9 and 3.4% of the dose administered in the first 24 h (Table 4), which is 6-20-fold lower than that measured after the i.v. administration of L-NDDP (21). This suggests that systemic absorption from the pleural cavity in 24 h is between 5 and 16% of the dose instilled.

**DISCUSSION**

The results of this study demonstrate that L-NDDP administered intrapleurally has a different toxicity profile and MTD compared to when it is administered i.v. (13). The MTD of intrapleural L-NDDP is 450 mg/m², and the dose-limiting toxicity is chemical pleuritis, whereas the MTD of L-NDDP i.v. is 300 mg/m², and the dose-limiting toxicity is myelosuppression, mainly granulocytopenia. These changes correlate with the differences found in the plasma pharmacokinetics. L-NDDP absorption into the systemic circulation from the pleural cavity is slow; peak levels of total platinum are reached at or after 24 h and are about 3-4-fold lower than those achieved after the i.v. administration over 4 h of a 50% lower dose. L-NDDP produced a fluid loculation effect in 13 of 21 patients of >50% reduction in the amount of baseline pleural fluid in 7 of 21 patients (33%).

Pleurodesis is a very effective way to palliate the symptoms, mostly dyspnea, caused by malignant pleural effusions by preventing fluid reaccumulation, thus avoiding the need for frequent thoracentesis. When a pleural effusion is a manifestation of...
distant metastatic spread from an extrathoracic malignancy or locally advanced lung cancer, local antitumor therapy in the form of surgery, radiotherapy, or even intrapleural therapy is not indicated, and the treatment of choice is systemic chemotherapy. MPM is a disease in which intrapleural chemotherapy as a local form of antitumor therapy may have a role in some cases because the disease tends to remain confined to the pleural cavity (1, 2), causes the death of the patients as a result of local growth, and does not respond to systemic chemotherapy (23, 24).

Antitumor drugs designed or intended for intracavitary therapy should have two properties: (a) prolonged residence time in the cavity and, therefore, delayed absorption into the systemic circulation to keep the peak systemic drug levels within a subtherapeutic or subtoxic range; and (b) ability to penetrate easily into the tumor tissue from its surface, like in the case of any topical therapy. An agent ideally suited for intracavitary therapy should not have a systemic effect at doses that exert an optimal local antitumor effect. If a systemic effect was needed in addition to an optimized local effect, this could be accomplished by combining the intrapleural therapy with i.v. systemic therapy using conventional agents. Intracavitary chemotherapy has been studied extensively in the other human malignancy apart from MPM, which tends to remain confined to a body cavity, like OV carcinoma (25, 26). Recently, the administration of i.p. cisplatin was reported to increase the cure rate of patients with OV carcinoma with minimal residual disease after debulking surgery by about 10% when compared with i.v. cisplatin in a large randomized trial (27). The results of this study are more impressive when one takes into account that cisplatin is not an ideal agent for intracavitary therapy because of its fast absorption into the circulation and poor tissue penetration ability. Cisplatin administered i.p. and intrapleurally is rapidly absorbed into the systemic circulation; peak plasma levels are reached at 20–30 min and are similar to those of a 2-h i.v. infusion, and all drug is absorbed within 4 h (10, 28).

Of this rapid absorption, the intracavity cisplatin AUC is higher than the plasma AUC, thus conferring the potential for an enhanced intracavitary antitumor effect. As a result, i.p. cisplatin preserves its systemic toxicity and also its systemic antitumor activity and has an enhanced intracavitary antitumor effect. L-NDDP is a lipophilic and non-cross-resistant platinum compound that is naturally formulated in large multilamellar liposomes (11). Because of its lipophilicity, its transmembrane transport has been shown to be much higher than that of cisplatin (14, 15), and its tissue penetration properties should be markedly enhanced (29). Because of the large liposomes used to deliver NDDP, its residence time in the peritoneal cavity was found to be much more prolonged than that of cisplatin in rats (19). In view of these properties, the observation of intolerable local toxicity in the absence of systemic toxicity with the intrapleural administration of L-NDDP in humans shown by the current study is not surprising and suggests that it may have a potential for use as a local intrapleural anticancer therapy. In addition, the control of the pleural effusion observed in about one-third of the patients, particularly those with MPM, suggests that MPM, because of its tendency to remain localized in the pleural cavity, may be a reasonable indication for an agent the biological effects of which are confined also to the pleural cavity when administered locally.

Chemical pleuritis manifested by chest pain was the limiting toxicity of L-NDDP. At least in one case, the last patient treated, we were able to demonstrate that chemical pleuritis caused a rapid fluid reaccumulation. In a few patients, we also observed initial pleural fluid loculation without reduction in the amount of fluid and subsequently a continued decrease in the amount of loculated pleural fluid over a period of months. One of these patients ended up with minimal residual pleural thickening and has not had recurrence of the pleural effusion in 21 months. This observation further supports the concept that L-NDDP initially causes a chemical pleuritis that can be associated with fluid reaccumulation and that resolves slowly, over a period of weeks or even months.

The absorption of L-NDDP into the systemic circulation was clearly biphasic, with an initial phase lasting 2 h of fast absorption followed by a phase of slow but steady absorption lasting at least up to 24 h. The initial phase may correspond to direct drug absorption through the pleura capillaries, whereas the delayed absorption may correspond to drug reaching the systemic circulation through the lymphatic channels. Unfortunately, no pleural fluid levels could be obtained in the present study, and therefore, the proportion of drug that remains in the cavity or that is in transit toward the systemic circulation via the

![Figure 2](https://example.com/figure2.png)

**Figure 2**: Mean plasma total ( ), methanol-extractable ( ), and ultrafilterable ( ) platinum (Pt) in four patients treated with 550 mg/m² L-NDDP intrapleurally.

### Table 5

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>6 h Ultrafilterable Pt (% total plasma Pt)</th>
<th>24 h Ultrafilterable Pt (% total plasma Pt)</th>
<th>6 h Methanol-extractable Pt (% total plasma Pt)</th>
<th>24 h Methanol-extractable Pt (% total plasma Pt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24.2</td>
<td>10.1</td>
<td>33.7</td>
<td>12.6</td>
</tr>
<tr>
<td>2</td>
<td>15.8</td>
<td>14.1</td>
<td>41.6</td>
<td>25.2</td>
</tr>
<tr>
<td>3</td>
<td>18.5</td>
<td>12.1</td>
<td>31.2</td>
<td>18.2</td>
</tr>
<tr>
<td>4</td>
<td>18.5</td>
<td>10.8</td>
<td>31.2</td>
<td>19.8</td>
</tr>
<tr>
<td>Mean</td>
<td>19.5 ± 4.3</td>
<td>11.8 ± 1.8</td>
<td>35.5 ± 5.4</td>
<td>19.0 ± 5.2</td>
</tr>
</tbody>
</table>
lymphatic system at each time point is unknown. However, comparison of urinary excretion in patients receiving systemic L-NDDP (22) and intrapleural L-NDDP suggests that the major part of the drug may be present in the cavity at 24 h.

In summary, this study shows that the intrapleural administration of a dose of 450 mg/m² of L-NDDP is safe and that the biological activity of L-NDDP administered intrapleurally is confined to the pleural cavity. Because of the safety profile and the control of the pleural effusion in some patients with MPM, a disease for which no effective therapy exists (30, 31), a Phase II study of intrapleural L-NDDP in patients with MPM is planned. Because the ability of L-NDDP to penetrate in depth into the tumor tissue is likely to be a major determinant of its effect, thoracoscopic evaluation of the bulkiness of the disease will be performed in all patients entered into this study.

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REFERENCES


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