Liposomal cisplatin: a new cisplatin formulation

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Over the last three decades, cisplatin has been one of the most effective cytotoxic agents, but its administration has been hindered by its nephrotoxicity, neurotoxicity and myelo toxicity. Recently, liposomal cisplatin, lipoplatin, has been formulated and tested thoroughly in preclinical (*in vitro*) and phase I, II and III trials, as documented in the literature. Experiments in animals showed that lipoplatin is less toxic than cisplatin and that it produces tumour reduction. The histological examination of treated tumours from mouse xenografts was consistent with apoptosis in the tumour cells in a mechanism similar to that of cisplatin. Lipoplatin infusion in patients and measurements of platinum levels in tumour specimens showed 10–50 times higher levels in tumours and metastases than in the adjacent normal specimens. A phase I–II study using a combination of lipoplatin and gemcitabine in pretreated patients (with disease progression or stable disease) with advanced pancreatic cancer was conducted. No nephrotoxicity was observed. With lipoplatin monotherapy the dose-limiting toxicity was determined to be 350 mg/m^2 and the maximum tolerated dose 300 mg/m^2; when used in combination with paclitaxel the dose-limiting toxicity for lipoplatin was 250 mg/m^2 and for paclitaxel 175 mg/m^2, and the maximum tolerated dose was 200 and 175 mg/m^2, respectively. In two phase II randomized studies comparing the lipoplatin combination versus the cisplatin combination, it was found that the former was statistically significantly less toxic than the latter, whereas the response rate and survival were similar. Up to now, the data on lipoplatin treatment in malignant tumours are quite impressive, because of the negligible toxicity and because it is equal if not superior to cisplatin with regard to response rate. This review aims to chronologically document publications relevant to liposomal cisplatin to date. *Anti-Cancer Drugs* 21:732–736 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Cisplatin [cis-$PtCl_2(NH_3)_2$] has been used worldwide, mainly for the treatment of head and neck, lung, gastrointestinal (GI), ovarian, bladder and testicular cancers. One of the most effective cytotoxic agents in clinical practice, cisplatin is administered in combination with a second and occasionally a third cytotoxic drug [1–7]. Cisplatin, although very effective, has been associated with side effects including nephrotoxicity [8]. Extensive clinical use has been impeded by adverse reactions, occasionally severe. Apart from mild and severe renal and GI toxicity, peripheral neuropathy, asthenia and ototoxicity have also been commonly observed [7–13]. The risk of nephrotoxicity caused by cisplatin frequently hinders the use of higher doses that would maximize its antineoplastic effects [13,14]. Cisplatin is not particularly myelotoxic. Over the years, there have been attempts to find a substitute for cisplatin, mainly using its analogue carboplatin [15,16]. Carboplatin and oxaliplatin have been used, but as yet neither of these analogues has achieved superior effectiveness to cisplatin [16,17]. Other cytotoxic agents used as substitutes were taxanes (paclitaxel and docetaxel), gemcitabine, vinorelbine, pemetrexed and irinotecan [18–25].

A new cytotoxic formulation of cisplatin, liposomal cisplatin, has recently been produced. Liposomal cisplatin (Lipoplatin; Regulon Inc., Mountain View, California, USA) is another agent whose use over the last years is ongoing in trials. This new liposomal formulation is formed from cisplatin and liposomes consisting of dipalmitoyl phosphatidyl glycerol, soyphosphatidyl choline cholesterol and methoxypolythylene glycol-distrearoyl phosphatidylethanolamine. Lipoplatin was developed to reduce the systemic toxicity of cisplatin while simultaneously improving the targeting of the drug to the primary tumour and to metastases by enhancing the half-life and thus its circulation time in body fluids and tissues.

Preclinical data

Experiments in animals showed that lipoplatin is less toxic than cisplatin and that it also achieved tumour reduction. This was detected in human breast MCF-7 or prostate LNCaP xenografts that were intraperitoneally or intravenously injected into animals [26]. Histological examination of treated tumours from mouse xenografts was consistent with apoptosis in the tumour cells in a mechanism similar to that of cisplatin. Mice and rats

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injected with cisplatin developed renal insufficiency with clear evidence of tubular damage, but those injected with the same dose of lipoplatin were free of kidney injury [27]. Another preclinical study was performed to test lipoplatin versus cisplatin with respect to cytotoxicity. This study involved established cell lines derived from non-small cell lung cancer, renal cell carcinoma and normal haematopoietic cell precursors to identify the biological markers associated with sensitivity and resistance [28]. The drugs were used at scalar concentrations of 0.1, 1, 10 and 20 μmol/l for exposure times corresponding to half-life values in humans, that is, 6 h for cisplatin and 72 h for lipoplatin, followed by a 72 h culture in a drug-free medium (washout). The cytotoxic effect was evaluated at the end of the washout time. DNA was analysed by real-time-PCR) to detect the expression of multidrug resistance 1, excision repair cross-complementing 1, lung resistance protein and b2-microglobulin. It was shown that lipoplatin had a higher antitumour activity in both tumour histotypes and that it was safer than the parent compound cisplatin.

Formulation characteristics

Lipoplatin is composed of 8.9% cisplatin and 91.1% lipids (ratio 0.9/9.1). Repeated extrusions are performed with nitrogen pressure through filters for downsizing its nanoparticles during manufacturing. Although it is light-sensitive, the lipoplatin formulation seems to be light-resistant, presumably because liposomes shield the drug.

Clinical studies

A phase I study was performed with the objective of investigating the pharmacokinetics and toxicity of liposomal cisplatin [29]. Twenty-seven patients were included for dosage escalation, 3–5 patients at each dosage level. The levels started at 25 mg/m^2 and were increased by 25 mg up to 125 mg/m^2. Three patients were also treated at higher dose levels, one each at 200, 250 and 300 mg/m^2. The measurements of platinum levels in the patients' plasma as a function of time showed that a maximum platinum level (of lipoplatin) is attained at 6–8 h (half-life). The duration of the release of lipoplatin from the blood was 60–117 h depending on the dose. Urine excretion reached 40% of the infused dose in 3 days. These data show that lipoplatin up to a dose of 125 mg/m^2 administered once every 14 days has no nephrotoxicity and that it lacks the serious side effects of cisplatin [29].

A polyethylene-glycol coating of the liposome nanoparticles is supposed to result in tumour accumulation of the drug by extravasation through the altered tumour vasculature. Another study explored the hypothesis that the intravenous infusion of lipoplatin results in tumour targeting. The patients' tumour material (specimens and normal tissues) was taken during the operation, which took place approximately 20 h after lipoplatin infusion. The direct measurements of the platinum levels (part of lipoplatin) in the specimens from the excised tumour and from the normal tissues showed that the total platinum levels were on average 10–50 times higher in malignant tissue compared with the adjacent normal tissue specimens. The most effective targeting was observed in colon cancer, with an accumulation of up to 200-fold higher in colon tumours compared with normal colon tissue. Gastric tumours displayed the highest levels of total platinum, suggesting lipoplatin as a candidate anticancer agent for gastric tumours [30].

The above data were considered adequate to begin administering lipoplatin to patients with resistant tumours or to those nonresponsive to first-line chemotherapy. A phase I–II study [31] was performed with liposomal cisplatin combined with gemcitabine in patients with pretreated advanced pancreatic cancer; all of the patients had been pretreated with gemcitabine monotherapy and at the time the trial started, the patients had mainly stable or progressive disease. The combination of the two agents began with a low dose of lipoplatin (25 mg/m^2) escalating to 50, 75, 100 and 125 mg/m^2, whereas the dose of gemcitabine remained the same (1000 mg/m^2) for all levels of lipoplatin escalation. Grade 2 neutropenia was observed at the lipoplatin doses of 100 and 125 mg/m^2, as were grade 1 with nausea/vomiting, fatigue diarrhoea, neurotoxicity and thrombotic episodes. No nephrotoxicity was observed. A partial response rate was achieved in 2 out of the 24 patients (8.3%). The results of this trial were not considered definitive as far as the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) were concerned, as further investigation of the MTD and DLT of lipoplatin as a single agent or in combination with another cytotoxic agent was required.

Another phase I trial was performed using a combination of lipoplatin and gemcitabine in patients with non-small cell lung cancer. All patients had been pretreated with cisplatin-based chemotherapy and were considered refractory to chemotherapy when recruited. Both the agents were administered on days 1 and 8, and again on day 21. Owing to grade 3–4 myelotoxicity at a 130 mg/m^2 dose of lipoplatin in three out of the four patients, these investigators determined that the DLT could also be 130 mg/m^2. Gemcitabine administered on days 1 and 8 in combination with another agent is known to produce a high percentage of grade 2–4 myelotoxicity; therefore, the finding of myelotoxicity in the aforementioned trial should not be attributed to lipoplatin, but rather mainly to gemcitabine. This study was underpowered, as the number of patients was only 13 [32]. Again, the MTD and DLT were not yet defined. The determination of the MTD and DLT was necessary to assist future investigators in administering the correct MTD.

A phase III trial combining lipoplatin with 5-fluorouracil (5-FU) and comparing cisplatin with 5-FU was carried out in patients with advanced head and neck cancer. The

pharmacokinetics were investigated and it was concluded that the terminal half-life was approximately half as long for lipoplatin (10.98/h) compared with cisplatin (24.5 h). Even though the maximum observed concentration in the plasma was greater for lipoplatin than for cisplatin, the area under the concentration time-curve was less (6.5 vs. 4.07 and 66.85 vs. 130.33 μg/h/ml, respectively). These investigators concluded that the pharmacokinetic profile of lipoplatin (in combination with 5-FU) suggests that the liposomal formulation results in a greater body clearance and shorter half-life than conventional cisplatin, which thus confirms the clinical observation of decreased toxicity, especially renal deterioration [33].

A trial was performed in which a comparison of toxicity between liposomal cisplatin and cisplatin, both combined with 5-FU, was made in patients with squamous cell carcinoma of the head and neck; the evaluation involved quite a small number of patients (43 patients randomized into two arms). It was found that liposomal cisplatin seems to reduce both renal and haematological toxicity to a clinically relevant extent compared with conventional cisplatin. These investigators commented that this reduction in side effects will influence the preservation of the dose density of the chemotherapy, and thereby the efficacy of the treatment [34].

A phase II study combining lipoplatin with vinorelbine in the first-line treatment of HER2/neu-negative metastatic breast cancer was performed. The investigators administered the lipoplatin–vinorelbine combination on the basis of the rationale that the frequent use of antracyclines and taxanes in the adjuvant setting of breast cancer has led to drug resistance and cardiac toxicity. This raised the need for new agents in the metastatic setting. Another reason for testing the aforementioned combination was that the use of cisplatin–vinorelbine showed interesting results with an overall response rate of 64%. Lipoplatin became a non-toxic alternative agent to cisplatin. Twenty-six out of the 35 treated patients were analysed. The dose of lipoplatin was 120 mg/m^2 on days 1, 8 and 15 and the dose of vinorelbine was 30 mg/m^2 on days 1 and 8, every 3 weeks for six cycles. An objective tumour response was observed in 11 out of the 22 evaluable patients (50%) and there was one complete response (4.5%). Ten patients (45.5%) had stable disease. No WHO grade 3–4 nephrotoxicity or neuropathy was observed. Febrile neutropenia developed in 11.5% of the patients. I would surmise that the neutropenia was a result of vinorelbine. The investigators concluded that the lipoplatin and vinorelbine combination shows promising activity and good tolerance [35].

After quite adequate pharmacokinetic testing of liposomal cisplatin in phase I and II trials, in combination with a second cytotoxic agent, it became necessary to investigate lipoplatin in phase II and III randomized trials. The main aim was to determine whether there was a difference between lipoplatin and cisplatin with respect to efficacy and safety.

In all of the studies reported here, the dose of liposomal cisplatin administered was not the MTD. For this reason, another recent phase I trial was carried out to determine whether a dosage higher than 120 mg/m^2 was sufficient to establish the MTD. The lack of myelotoxicity and nephrotoxicity permitted the administration of lipoplatin every 2 weeks (instead of every 3 weeks); this allowed a second cytotoxic agent to be administered, provided that agent was one whereby myelotoxicity would recover within 2 weeks (i.e. the great majority of chemotherapeutic drugs).

The phase I trial that is described next included single-lipoplatin dose escalation and a combination of lipoplatin and paclitaxel, both drugs administered at escalating dose levels [36]. Eight dose levels in total were tested with lipoplatin monotherapy. The dosage began at 125 mg/m^2, increased by 25–50 mg/m^2 and was escalated up to 350 mg/m^2 per level, in 39 patients (four patients per level). For levels up to 300 mg/m^2 the main toxicity was grade 2 nausea/vomiting and fatigue in 75% of the patients, and neutropenia and nephrotoxicity in 25% of the patients. At a dose of 350 mg/m^2, 25% of the patients presented with grade 3 neutropenia and nephrotoxicity; 350 mg/m^2 was then considered to be the DLT. The MTD was determined to be 300 mg/m^2 as a monotherapy treatment. With regard to the combination of lipoplatin and paclitaxel, an agent that is myelotoxic but not nephrotoxic, the escalation of the two drugs was from 100 mg/m^2 increased by 50 mg/m^2 up to 250 mg/m^2, four levels, for lipoplatin, and from 100 up to 175 mg/m^2, three levels, for paclitaxel. Twenty-seven patients were included. At a dose level of 250 mg/m^2 of lipoplatin and 175 mg/m^2 of paclitaxel, half of the patients presented with grade 2 neurotoxicity, nausea and vomiting, fatigue and neutropenia. Grade 3 neurotoxicity was observed in two out of the four patients. At a dose level of 200 mg/m^2 of lipoplatin and 175 mg/m^2 of paclitaxel, grade 2 neurotoxicity was observed in two out of the four patients and nausea/vomiting, fatigue and neutropenia in one out of the four patients. The DLT was determined to be 250 mg/m^2 of lipoplatin and 175 mg/m^2 of paclitaxel and the MTD was determined to be 200 mg/m^2 of lipoplatin and 175 mg/m^2 of paclitaxel. If the treatment was to be administered every 2 weeks, the MTD was 200 mg/m^2 of lipoplatin and 135 mg/m^2 of paclitaxel [36]. After the aforementioned phase I trial, the dosage of lipoplatin when combined with another cytotoxic agent was suggested to be 200 mg/m^2 for future trials.

Two trials whose target was to compare the efficacy and safety of lipoplatin in combination with another cytotoxic agent versus cisplatin with the same second agent were recently published. One of these two trials was a phase II randomized study comparing the combination of lipoplatin

(120 mg/m^2) and gemcitabine (1000 mg/m^2), the former administered on days 1, 8, 15 and the latter on days 1 and 8 repeated every 3 weeks. Eighty-eight patients, 47 in the lipoplatin group and 41 in the cisplatin group, were included. The response rate was 31.7 and 25.6% for the lipoplatin and cisplatin groups, respectively. The disease control rate was superior for the group that received lipoplatin. There was a significant reduction in nephrotoxicity in the patients who received lipoplatin–gemcitabine versus those who were administered cisplatin–gemcitabine, and the difference was statistically significant ($P < 0.001$) [37].

The second study whose objective was to compare liposomal cisplatin combined with paclitaxel versus cisplatin also combined with paclitaxel was reported in the literature recently. The main objective was to determine safety and nephrotoxicity, GI side effects, peripheral neuropathy and hematologic toxicity. The secondary objective was to determine the response rate, survival and time to tumour progression. This was a phase III randomized multicentre trial in which 229 patients were divided in two arms. Arm A received lipoplatin and paclitaxel and arm B cisplatin and paclitaxel. There was a statistically significant difference in some of the most important adverse reactions in favour of the lipoplatin arm: nephrotoxicity was significantly reduced ($P < 0.001$), as were leucopenia (P 0.0170) and other side effects, that is, GI tract nausea/vomiting (P 0.042) and asthenia (P 0.019). With regard to other adverse reactions, such as neurotoxicity, thrombocytopenia, diarrhoea and alopecia, no statistically significant difference was determined. Most of the latter adverse reactions were attributed mainly to paclitaxel. There were no statistically significant differences between the two arms with regard to the secondary objectives, that is, median survival, overall survival and time to tumour progression. The response rate was higher with the administration of liposomal–paclitaxel (58.8%) versus cisplatin–paclitaxel (47%), approaching a statistically significant difference (P 0.073) [38].

An interesting finding was observed in both of the latter two studies: there was a difference in the response rate between the lipoplatin group and the cisplatin group in patients with adenocarcinomas of the lungs in favour of lipoplatin, but there was no response rate difference found in the patients with squamous cell-type cancer. A recently integrated randomized trial was presented at American Society of Clinical Oncology 2010: lipoplatin combined with paclitaxel was compared with cisplatin combined with paclitaxel in patients with adenocarcinoma and undifferentiated histological types of lung cancer. There was a statistically significant difference in the response rate in favour of the patients who received lipoplatin versus those who received cisplatin (P 0.036) [39]. Although liposomal cisplatin has been investigated in pancreatic, head and neck and breast cancers, the main research is in non-small cell lung cancer. To date it has been assumed, on the basis of data in the literature, that the efficacy of liposomal cisplatin is similar to that of cisplatin but that there is a great reduction in the different toxicities, the most important being a lack of nephrotoxicity. This observation has been confirmed in all the published data to date. Lipoplatin is a promising new cytotoxic agent that seems to be the least toxic cisplatin formulation, but further studies are needed for it to become an established agent in the treatment of cancer.

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