Exploring novel formulations and new classes of anticancer drugs in solid tumors

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3

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Early cessation of the clinical development of LiPlaCis, a liposomal cisplatin formulation

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ABSTRACT

Purpose

To evaluate the safety and tolerability of LiPlaCis, a liposomal formulated platinum compound, in patients with solid tumors and to determine the maximum tolerated dose (MTD) of intravenous (i.v.) LiPlaCis and to assess plasma and urine pharmacokinetics and plasma biomarkers.

Patients and methods

Patients with solid tumors without standard therapeutic options were enrolled to receive LiPlaCis administered as a 1 h infusion without additional hydration every 3 weeks until RECIST progression or unacceptable toxicity. Cohorts of 3-6 patients were treated at each dose level until MTD was reached.

Results

Eighteen patients were enrolled and 64 cycles were delivered. At the first dose level 3 patients experienced an infusion reaction. Despite prophylactic premedication and prolongation of the infusion to 2 h in further patients, three other patients had mild acute infusion reactions. Toxicity at the fifth dose level of 120 mg consisted of grade 2 renal toxicity, reversible after hydration in 2 patients and grade 4 thrombocytopenia in one of these patients. Peak plasma concentrations and AUC were dose proportional. The interpatient variability in the clearance of total LiPlaCis-derived platinum was 41%. Platinum was excreted via the urine mainly during the first 24 h after administration. Investigated plasma biomarkers $sPLA_2$ and SC5b-9 were related to, but not predictive for, acute infusion reactions.

Conclusion

The observed safety profile suggests no benefit over standard cisplatin formulations and LiPlaCis will require reformulation to enable further development.

INTRODUCTION

Cisplatin-based anticancer therapies are widely used in the treatment of solid tumors. Dose-limiting toxicities include renal-tubular dysfunction, peripheral-neuropathy and ototoxicity, the first of which is due to rapid renal clearance of cisplatin and can be largely prevented by extensive pre- and post-hydration surrounding cisplatin administration.[1-3]

Widening cisplatin's therapeutic window by making the drug more tumor selective seems attractive. Liposomal drug delivery could serve this purpose, but was previously limited by the fast clearance from the blood. Addition of polyethylene glycol to the surface of liposomes resolved this problem and leads to preferential trapping and accumulation of liposomes in the leaky tumor vasculature resulting in enhanced drug exposure at the tumor site.[4]

However, in particular true for hydrophilic drugs like cisplatin, which cannot readily pass the liposomal lipid membrane, liposomal degradation and subsequent drug release into the tumor is an essential prerequisite for effect. The absence of drug release from the liposomes and the resulting absence of DNA-adduct formation, explained the lack of activity of SPI-077, a liposomal cisplatin formulation.[5,6]

LiPlaCis is a novel liposomal formulation of cisplatin. The LiPlaCis liposomes (i.e. LiPlasomes) are designed to be degraded by secretory phospholipase A_2 (PLA_2), a relatively tumor selective enzyme and thereby release the encapsulated cisplatin.[7,8] The use of enzymes, such as PLA_2, for triggered-drug release provides a novel tumor selective drug delivery approach. Preclinical proof of principle has been demonstrated *in vitro* and *in vivo*.[9,10]

The aim of this study was to define the maximum tolerated dose (MTD), the recommended phase II dose, pharmacokinetics and pharmacodynamics, as well as the preliminarily antitumor effects of a three-weekly schedule of LiPlaCis in patients with solid tumors.

PATIENTS AND METHODS

Drug formulation

This study was an open-label, dose-escalating phase I study of LiPlaCis in patients with advanced solid tumors. LiPlaCis was supplied by LiPlasome Pharma A/S as a concentrate for infusion in vials containing 2 mL (1 mg/mL) each as a white opalescent dispersion. The product must be stored at T = -80°C in order to ensure stabilization of the liposomes. The liposomes of LiPlaCis are composed of 1,2-disteaeoyl-*sn*-glycero-3-phosphocholine,1,2-

distearoyl-*sn*-glycero-3-[phosphor-*rac*-(1-glycerol)] (sodium salt) and 1,2-disteaeoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (ammonium salt). In addition, sodium chloride, sucrose and disodium hydrogen phosphate are added to stabilize the liposomes. After thawing in a water bath at room temperature the content of the vials was added to a polyvinylchloride bag with saline to a total volume of 500 mL. The solution was kept at room temperature protected from light until administration which had to take place within 8 h after preparation.

Study design

LiPlaCis was administered intravenously in 1 h once every 3 weeks as long as there was no evidence of progressive disease (PD) or unacceptable toxicity. Escalation followed in a 3 + 3 design with increase of 20-100% from the previous dose level based on toxicity and pharmacokinetics. The MTD was defined as the dose with two or more patients with dose-limiting toxicity (DLT) in a cohort of 3 or 6 patients. Toxicity was evaluated using the CTC version 3.0.[11] DLT was defined as CTC grade 4 neutropenia, grade 4 thrombocytopenia, or grade 3 thrombocytopenia complicated with bleeding, persistent grade 2 neurotoxicity, persistent serum creatinine $> 2 \times$ upper limit of normal (ULN), drug-related non-hematological grade 3-4 toxicity or a delay in re-treatment with LiPlaCis of more than 2 weeks. The recommended dose for phase II (RD) was defined as the immediate-dose level below MTD.

If 2 patients at any dose level experienced an infusion reaction of at least grade 2, reduction in infusion rate and premedication would be introduced. No prophylactic anti-emetics were administered. Once 2 patients experienced nausea or vomiting grade 2 or more, prophylactic use of anti-emetics would be introduced for both the patients in question and the remaining patients. Hydration was not used routinely, however if nephrotoxicity was observed in a patient, both pre- and post-hydration would be introduced for the remaining cycles of this patient. In case of nephrotoxicity in multiple patients, a routine pre- and post-hydration schedule was to be implemented. Patients with measurable disease were assessed for antitumor activity by RECIST every 3 cycles and patients without measurable disease were assessed clinically.[12] Each subject, receiving at least 1 cycle was assigned a best response. The analysis of safety was based on the subjects who received at least one dose of LiPlaCis.

Eligibility criteria

Eligibility included a histological- or cytological-documented locally advanced or metastatic solid tumor refractory to standard therapy or for which no effective therapy existed and ECOG performance status 0-2. Required laboratory values included: absolute neutrophil count > 1.5×10^9/L, platelet count > 100×10^9/L, hemoglobin > 9 g/dL, total bilirubin < $1.5 \times$ ULN, alkaline phosphatase < $2.5 \times$ ULN, creatinine and blood urea within normal limits, unless creatinine clearance was < 60 mL/min calculated according to Cockcroft–Gault formula, aspartate aminotransferase and alanine aminotransferase < $2.5 \times$ ULN, or < $5 \times$ ULN in case of liver metastases. The study was approved by the institutional ethical committee and patients gave written informed consent prior to treatment.

Pharmacokinetics and pharmacodynamics

Serial blood samples for plasma total LiPlaCis-derived platinum (i.e. cisplatin-derived liposomal- associated plus non-liposomal associated platinum) concentration measurements as well as for secretory phospholipase A_2 ($sPLA_2$) and the complement activation marker SC5b-9 were collected over a 5-d period following the start of the infusion in cycle 1. Blood-samples were collected in standard blood collection lithium-heparin tubes prior to LiPlaCis infusion, halfway the infusion, 5 min before the end of infusion and 30 min, 1, 3, 6, 8, 24, 47, 71 and 95 h after the end of infusion. In case the infusion was stopped due to an acute infusion reaction, additional blood samples were collected at the point of interruption and restart of the infusion. Samples were centrifuged within 10 min after collection at 2800-3000 g for 10 min at 4°C. The plasma supernatant was stored at T < -70°C upon analysis.

Urine samples for the analysis of LiPlaCis-derived platinum concentrations were collected as voided in standard polypropylene containers prior to start of the infusion and during the following period after start of infusion: 0-6, 6-12, 12-24, 24-48, 48-72 and 72-96 h. The total volume was recorded and 3-mL aliquot of each portion stored at T < -70°C upon analysis.

Total LiPlaCis-derived platinum was determined by a validated, atomic absorption spectrophotometer method for cisplatin-derived platinum, with a lower limit of quantitation established at 0.200 µg/mL, essentially reported previously.[13] Pharmacokinetic parameter estimates of platinum were derived from weighted ($1/y$) two-compartmental model analysis using WinNonlin version 5.2.1 (Pharsight Corp., Mountain View, CA; model 10). Urine concentrations of total LiPlaCis-derived platinum were determined likewise. The lower limit of quantitation was validated at 1.00 µg/mL platinum in urine.

Plasma concentrations of $sPLA_2$ were determined by an enzyme immunoassay (EIA) based on the double-antibody 'sandwich' technique specific for type IIa $sPLA_2$ ($sPLA_2$ human Type IIA EIA Kit, Cayman, Ann Arbor, Michigan, United States of America (USA)). Plasma samples were also analyzed for SC5b-9, the terminal complement complex (TCC, SC5b-9) generated by the assembly of C5 through C9 as a consequence of activation of the complement system, using a SC5b-9 Plus EIA Kit (Quidel, San Diego CA, USA). ELISA measurements were performed according to the manufacturer's protocols.

Statistical analysis

Statistical analysis was performed using SPSS version 15.0. Potential differences in PK parameters between subgroups of patients were evaluated with ANOVA and *T*-test, whilst correlations were tested with linear regression analysis.

RESULTS

Patients, doses and toxicity

From May 2008 to November 2009 18 patients were enrolled into this study. Baseline patient demographics and disease characteristics are outlined in Table 3.1.

Overall, a total of 64 cycles of LiPlaCis were administered with a median of 3 cycles per patient (range 1-15). Three patients were treated at the first dose level of 10 mg with one infusion reaction grade 2. Therefore three additional patients were enrolled at dose level 1. In one of them a grade 2 infusion reaction occurred within a few minutes of starting the first infusion, but without significant systemic reactions. After administration of clemastine and dexamethasone, the patients received the remainder of the infusion successfully. Due to the fact that 2 patients experienced a > grade 2 reaction requiring treatment, reduction of infusion rate to 50% and routine premedication with a combination of clemastine 2 mg i.v. and dexamethasone 10 mg i.v., were introduced. Three patients were treated at dose levels 2-5 (20, 40, 80 and 120 mg), without first cycle DLTs. At each dose level 2, 4 and 5, 1 patient had a grade 2 infusion reaction. The patient at dose level 4 experienced a recurrent-infusion reaction (grade 3) in the second cycle despite additional premedication and was taken off study. Grade 1-2 nephrotoxicity, reversible after hydration, was observed in 1 patient at the second dose level and 2 patients at the fifth dose level. At dose level 5, 1 patient had a DLT in the second cycle consisting of grade 4 thrombocytopenia, grade 2

Table 3.1 Baseline demographics and patient characteristics

Baseline characteristics	Patients (*n* (%))	
Gender		
Male	10	(55)
Female	8	(45)
Age, years		
Median (range)	58	(39-75)
ECOG performance status		
0	4	(22)
1	14	(78)
Tumor type		
Breast	2	(11)
Melanoma	2	(11)
Esophagus	2	(11)
Prostate	2	(11)
Parotic carcinoma	2	(11)
Oro-/hypopharyngeal cancer	2	(11)
Urothelial carcinoma	2	(11)
Other*	4	(22)

* = Adenoid cystic carcinoma, cancer of unknown primary, non-small cell lung cancer, sarcoma

renal toxicity and schistocytes based on hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) (Table 3.2). A second patient treated at this dose also developed a grade 2 renal toxicity in the first treatment cycle. Given the frequent infusion reactions and the high incidence of renal toxicity implicating no apparent practical benefit over standard formulated cisplatin it was concluded that without reformulation further development was precluded.

Response per RECIST was assessed in 12 patients, because 6 patients stopped treatment before their first planned disease evaluation after cycle 3 (2 patients on their own request, 2 because of recurrent infusion reactions and 2 because of DLT). Three from the 12 evaluable patients had stable disease (SD) at 9 weeks whereas the remaining 9 patients showed PD.

Pharmacokinetics

All 18 patients were evaluable for plasma-pharmacokinetic analysis. The observed plasma concentration, time data could be best fitted by a two-compartmental model in 17 patients,

whilst a one-compartmental model best fitted the data of 1 patient treated at the first dose-level of 10 mg, for which platinum could be quantitated only up to 8 h after end of infusion (i.e. platinum concentrations below 0.200 µg/mL). A summary of the pharmacokinetic parameters is presented in Table 3.3. Peak plasma concentrations were observed at or shortly after the end of infusion, irrespective of infuse duration. Peak plasma concentrations and

Table 3.2 Number of patients with treatment-related adverse events in all cycles

Adverse event		10 mg (*n* = 6)		20 mg (*n* = 3)		40 mg (*n* = 3)		80 mg (*n* = 3)		120 mg (*n* = 3)	
	Grade	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4	1-2	3-4
Leucopenia		1		1		1		1		–	
Neutropenia		–		–		–		–		–	
Thrombocytopenia		2		–		–		–		–	1
Anemia		3		3		1		2		2	
Nausea		3		2		1		2		2	
Vomiting		2		–		–		–		1	
Diarrhea		–		1		–		–		–	
Mucositis		–		–		–		1		–	
Nephrotoxicity		1		3		–		–		2	
Neurotoxicity		2		2		1		1		2	
Fatigue		4		3		2		1		2	
AST/ALT		4		1		1		1		2	
Infusion reaction		3		1		–		1[a]	1[a]	1	

[a] Same patient

Table 3.3 Mean ± SD plasma pharmacokinetics[a] of total LiPlaCis-derived platinum during course 1

Dose (mg)	Number of patients	C_{max}[b] (µg/mL)	$T_{1/2}\alpha$ (h)	$T_{1/2}\beta$ (h)	AUC (µg·h/mL)	CL (mL/h)	Vss (L)
10	6	1.62 ± 0.46	3.26 ± 0.56[c]	80 ± 21[c]	93.1 ± 31.8[c]	77.5 ± 29.6[c]	7.85 ± 0.81[c]
20	3	2.95 ± 0.32	3.44 ± 0.35	113 ± 46	258 ± 110	56.2 ± 21.1	7.91 ± 0.12
40	3	5.50 ± 1.18	5.50 ± 1.36	141 ± 59	559 ± 259	52.9 ± 20.7	9.21 ± 0.46
80	3	11.3 ± 0.23	3.98 ± 0.42	116 ± 35	888 ± 248	61.9 ± 18.5	9.31 ± 1.15
120	3	18.8 ± 7.50	5.04 ± 1.81	132 ± 90	2711 ± 2643	49.9 ± 34.1	6.43 ± 1.73
All	18	-	4.13 ± 1.26[d]	112 ± 51[d]	-	61.8 ± 25.3[d]	8.11 ± 1.34[d]

[a] Two-compartmental, except for 1 patient in 10 mg cohort which could be best fitted to a one-compartmental model

[b] Visually observed, in most cases (12 of 18) 0.5 or 1 h after end of infusion

[c] *n* = 5 (excluding patient fitted to one-compartmental model)

[d] *n* = 17 (excluding patient fitted to one-compartmental model)

AUC were dose-proportional. The interpatient variability in the clearance of total LiPlaCis-derived platinum was 41% and increased to 46% after correction for patient's individual body surface area. In addition, clearance was independent of gender ($P = 0.95$; *T*-test) and dose ($P = 0.59$; ANOVA) and was not related to age ($P = 0.94$; linear regression analysis). In Figure 3.1, the average total platinum concentration corrected for dose versus time curve is presented.

Platinum was below the lower limit of quantitation in most urine samples, especially at the lower dose-levels and after 24 h. Urinary excretion, however, seemed independent of the dose and if quantifiable, during the first 24 h after administration on average approximately 20% of the dose was excreted via the urine.

Pharmacodynamics

$sPLA_2$ levels could be analyzed in 17 patients and SC5b-9 levels in 14 patients. Plasma levels of $sPLA_2$ and SC5b-9 were readily detected in both baseline (pre-treatment) samples as well as on-therapy samples. Although the absolute $sPLA_2$ baseline plasma concentrations showed a high variability ranging from 1.5 to 13.7 ng/mL with a median of 6.3 ng/mL, relative $sPLA_2$ plasma levels were not affected upon administration of the liposomal- encapsulated cisplatin (LiPlaCis). The spectrum of SC5b-9 baseline levels displayed an even higher variation (range: 18-723 ng/mL; median: 233 ng/mL). All patients with a clinically-manifested acute infusion reaction showed an immediate increase in SC5b-9 levels after start of treatment

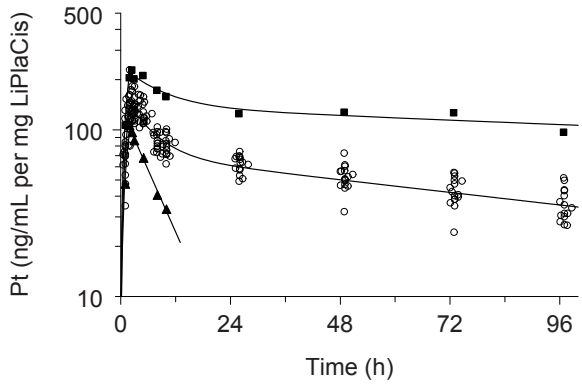

Figure 3.1 Average dose normalized concentration-time curve of LiPlaCis-derived platinum in plasma fitted to a two-compartmental model. The patients with the relative fast clearance (fitted to a one-compartmental model), treated at the first dose-level of 10 mg and the patient with the relative slow clearance, treated at the dose-level of 120 mg, are presented with the closed symbols.

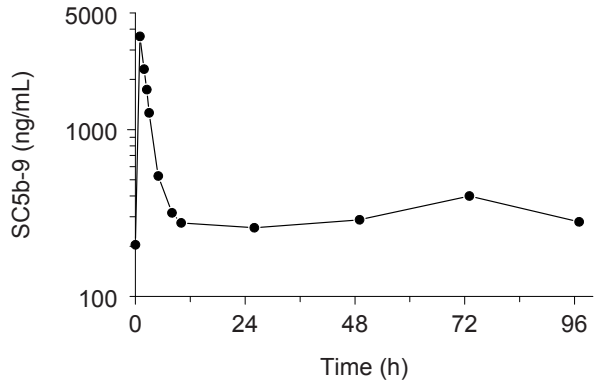

Figure 3.2 Plasma levels of the terminal complement complex (SC5b-9) in a typical representative patient with LiPlaCis infusion reaction. SC5b-9 concentrations were determined by ELISA in plasma samples before infusion with LiPlaCis (t = 0), halfway during the infusion (t = 60 min), 5 min before the end of infusion (t = 115 min) and at regular time points (30 min, 1, 3, 6, 8, 24, 47, 71 and 95 h) after end of infusion. Evidently, a clear increase in SC5b-9 levels was noted during and directly after LiPlaCis administration, indicative of the acute infusion reaction of this patient to LiPlaCis.

that returned to (pre-treatment) baseline within 24 h (Figure 3.2). However, the baseline $sPLA_2$ plasma levels in the patients with an acute infusion reaction (n = 5) did not differ from those observed in the other 12 patients (mean ± SD: 5.9 ± 1.5 ng/mL versus 7.5 ± 4.3 ng/mL; P = 0.42; T-test). Furthermore, no correlation was found between the baseline $sPLA_2$ levels and the plasma PK parameter $T_{1/2}\alpha$ (Pearson's coefficient correlation: r = 0.044; P = 0.87), indicating secretory PLA_2 levels are not associated with the plasma half-life of the LiPlasomes.

DISCUSSION

This study was designed to evaluate the tolerability, pharmacokinetics and pharmacodynamics of LiPlaCis, a novel liposomal formulation of cisplatin. LiPlaCis has a different toxicity profile compared to cisplatin; it seems to be less emetogenic at the dose levels studied. However, many patients experienced an acute infusion reaction related to the liposomal formulation requiring premedication with corticosteroids, which provides a disadvantage. Even more importantly, just like cisplatin, LiPlaCis induced renal toxicity and did not have the desired

kidney-sparing effect. The severity seemed to increase with the dose administered. Already at the dose level of 20 mg, grade 1 nephrotoxicity was observed in 3 patients 2 of which had confounding factors (pneumonia and nausea). The third patient had pre-existing grade 1 renal impairment. At the subsequent dose levels another 2 patients developed grade 1-2 renal toxicity. At the 120 mg dose level 2 patients developed grade 2 nephrotoxicity. In 1 patient this was due to HUS-TTP, which has been ascribed in the past to cisplatin-based chemotherapy, but is a rare side-effect.[14]

Lipoplatin, another liposomal-cisplatin formulation recently entered phase III studies. During the phase I study renal toxicity was not observed. The main toxicities of Lipoplatin constituted neutropenia, anemia and nausea and vomiting, all limited to grade 1-2.[15] In a subsequent phase Ib study combining Lipoplatin with 5-fluorouracil and radiotherapy 18% (2/11) of the patients developed grade 1 renal toxicity to which dehydration caused by gastrointestinal discomfort might have contributed.[16] This still contrasts the 33% (6/18) of the patients in our present study with LiPlaCis who developed renal toxicity.

Another major drawback of LiPlaCis was the frequent observation of non-dose related grade 2 infusion reactions despite premedication. Also after administration of Lipoplatin infusion reactions were observed albeit at an incidence of only 8.3%.[16] For pegylated-liposomal formulation of doxorubicin the percentage of acute infusion reaction is up to 9%.[17] This reaction that is typical for liposomal formulations, occurred at a rather (too) high incidence (7/18 patients, 39%) in our study. The infusion reactions were accompanied with complement activations, illustrated by an immediate increase in plasma SC5b-9 level (Figure 3.2).

Pharmacokinetic profiles of total LiPlaCis-derived platinum could be best fitted to a two-compartmental model. The initial half-life ($T_{1/2}\alpha$) most likely reflects the half-life of the intact circulating liposome, whilst the secondary half-life ($T_{1/2}\beta$) is considered to primarily reflect the half-life of extra-liposomal plasma-protein bound platinum. Although the LiPlasomes were constructed to be specifically degraded by $sPLA_2$ and plasma $sPLA_2$ concentrations were highly variable between patients, no correlation between the baseline levels of $sPLA_2$ and the initial half-life of LiPlaCis-derived platinum was observed. Potentially, other factors contributed to the degradation of the LiPlasomes. Total plasma-platinum clearance following LiPlaCis was slower compared to total-platinum clearance following the administration of free cisplatin and Lipoplatin, however was slightly faster compared to SPI-077 derived platinum.[15,18,19] Urinary excretion was slightly lower compared to free cisplatin and half of the excretion as observed after the administration of Lipoplatin.[15,20]

Although the toxicity pattern of LiPlaCis differed from cisplatin toxicity, renal damage was not prevented by the formulation. Acute infusion reactions required addition of extensive premedication that in turn could not completely prevent a high incidence of acute infusion reactions. Reformulation of LiPlaCis seems to be warranted prior to further development.

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