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Phase II study of liposomal cisplatin (Lipoplatin™) plus gemcitabine versus cisplatin plus gemcitabine as first line treatment in inoperable (stage IIIB/IV) non-small cell lung cancer

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ABSTRACT

Background: Lipoplatin is a new liposomal cisplatin designed to reduce cisplatin toxicities without reducing efficacy. In the present randomized phase II study, we examined the efficacy and safety of a Lipoplatin–gemcitabine versus a cisplatin–gemcitabine combination as first line treatment in advanced NSCLC.

Patients and methods: Patients with advanced (stages IIIB-IV) NSCLC received up to six 21-day cycles of Lipoplatin 120 mg/m^2 (days 1, 8, 15) and gemcitabine 1000 mg/m^2 (days 1 + 8) (arm A; LipoGem) versus cisplatin 100 mg/m^2 (day 1) and gemcitabine 1000 mg/m^2 (days 1 + 8) (arm B; CisGem). The primary objective was objective response rate (ORR). Secondary objectives were disease control rate (DCR), progression-free survival (PFS), duration of response and overall survival (OS). Another secondary objective was safety and tolerability of the LipoGem combination.

Results: Eighty-eight patients ($n = 88$) entered the study; 47 patients were treated with LipoGem versus 41 patients treated with CisGem. Efficacy was assessed in patients who completed at least 1 cycle of treatment; ORR was 31.7% in arm A versus 25.6% in arm B and DCR was 70.7% versus 56.4%, respectively. A preliminary efficacy of LipoGem versus CisGem in the adenocarcinoma histological subtype of NSCLC showed 16.7% versus 45.8% PD. Treatment in arm A was better tolerated with myelotoxicity and a transient mild elevation of serum creatinine as the dominant side effects; the only grade 4 adverse event was neutropenia noted in 2% of the patients. There was a significant reduction in nephrotoxicity in the LipoGem arm (0% versus 5% grade III, p-value < 0.001) as well as in nausea vomiting (2% versus 12% grade III, p-value < 0.001). In addition, less antiemetics and G-CSF were administered in arm A.

Conclusion: Overall, Lipoplatin appears to have lower toxicity, mainly renal toxicity as well as higher efficacy than cisplatin when combined with gemcitabine in advanced NSCLC.

1. Introduction

Lung cancer is the most common cause of cancer-related death in men and the second most common in women, while it is responsible for 1.3 million deaths worldwide annually and ~300,000 new cases in the EU [1,2]. Approximately 80% of lung cancer cases are non-small cell lung cancer (NSCLC) and in more than 70% of these cases, the disease is diagnosed at a late stage, when already locally advanced or metastatic. A number of chemotherapy regimens have been explored in clinical trials and in medical practice. For example, preferred regimens for first line treatment against NSCLC in EU include gemcitabine and cisplatin [3–5] and carboplatin–paclitaxel in USA [6,7]; second line treatments tested include single agents such as docetaxel [8,9], pemetrexed [10] and erlotinib [11] as well as combinations of gemcitabine plus docetaxel [12], gemcitabine and irrinotecan [13], docetaxel–ifosfamide–carboplatin [14].

One of the cytotoxic agents most commonly used in the treatment of NSCLC is cisplatin. The introduction and clinical development of cisplatin have been a milestone achievement in clinical

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oncology and has resulted in the cure of advanced testicular cancer patients [15–19]; cisplatin is recommended by FDA for testicular, ovarian, transitional cell bladder cancer, NSCLC (in combinations with gemcitabine), and cervical (in combination with radiation) cancers whereas its off-label use has been extended to other cancers as well [20–24]. However, its clinical use has been impeded by its severe toxicities, including nephrotoxicity [25–27], gastrointestinal toxicity, peripheral neuropathy [28–30] and ototoxicity [31,32]. The significant risk of cisplatin-induced nephrotoxicity frequently hinders the use of higher doses to maximize its antineoplastic effects.

Lipoplatin is a new liposomal cisplatin, designed to reduce cisplatin toxicities without reducing its efficacy [33]. Plasma pharmacokinetics and toxicity of Lipoplatin were studied in preclinical studies [33–35]. Animal studies comparing Lipoplatin with cisplatin showed Lipoplatin's reduced nephrotoxicity in rodents, whereas animals injected with cisplatin developed renal insufficiency with clear evidence of tubular damage; those injected with the same dose of Lipoplatin were almost completely free of kidney injury [34]. The observed superior cytotoxicity in all tumor cell models in combination with the much lower toxicity in normal cells for Lipoplatin compared with cisplatin, suggest a higher therapeutic index for Lipoplatin. Moreover, analysis of molecular markers known to be related to cisplatin resistance showed a direct correlation between cisplatin and Lipoplatin resistance and ERCC1 and LRP expression and was proposed as valid predictors of sensitivity or resistance to these drugs [36].

Following preclinical testing in animals, Lipoplatin entered clinical development in Europe in 2001. Pharmacokinetics, safety and efficacy were studied in several phase I and II studies [37–41]; half-life was shown to be between 30 and 50 h depending on the dose, in comparison to 6 h for cisplatin. There was no need for pre- or post-hydration during Lipoplatin administration contrary to cisplatin. Lipoplatin had a mild hematological and gastrointestinal toxicity but did not show any nephro- or neurotoxicity, and ototoxicity, it did not cause hair loss or fatigue and was void of most other side effects [37]. The drug was also used in the treatment of mesothelioma [42].

Nephrotoxicity and neurotoxicity, commonly reported in cisplatin treatment, were not seen at any dose level using single doses every 14 days; the Maximum Tolerated Dose (MTD) in combination with gemcitabine was defined at 120 mg/m^2 weekly. As a consequence, the purpose of this phase II study is to assess the efficacy and toxicity of Lipoplatin and gemcitabine in comparison with cisplatin and gemcitabine, a well-established doublet against advanced NSCLC.

2. Materials and methods

2.1. Drug

Lipoplatin is formed from cisplatin and liposomes composed of dipalmitoyl phosphatidyl glycerol (DPPG), soy phosphatidyl choline (SPC-3), cholesterol and methoxy-polyethylene glycol-distearoyl phosphatidylethanolamine (mPEG2000-DSPE).

2.2. Study design

This was a prospective, randomized, comparative, open-label, safety and efficacy phase II study. Primary objective was to evaluate the objective response rate (ORR). Secondary efficacy objectives were to estimate disease control rate (DCR), progression-free survival (PFS), duration of response and overall survival (OS). Another secondary objective was safety and tolerability of the combination.

The study protocol was approved by the local regulatory authorities and was conducted in accordance with Good Clinical Practice guidelines (GCP-ICH) and the ethical principles according to the Declaration of Helsinki.

2.3. Patients

Inclusion criteria included: age >18 years, with histologically or cytologically confirmed diagnosis of stage IIIb/IV NSCLC; ECOG performance status 0–1; at least one measurable lesion as defined by the RECIST criteria [43]; adequate bone marrow/liver/renal function; ability to provide written informed consent; ability to comply with the protocol. Only patients who were suitable candidates for chemotherapy alone were enrolled. Exclusion criteria included prior chemotherapy for NSCLC; other neoplasm; major surgery or radiotherapy within 3 weeks of study commencement; recent myocardial infarction or severe heart disease; autoimmune disease; pregnancy and lactation. Patients with brain metastases were eligible at least 1 month after the completion of radiotherapy and only if the lesion was evaluated as controlled.

2.4. Study treatment

Patients randomized to arm A, received Lipoplatin 120 mg/m^2 as a 6-h (intravenous) IV infusion on days 1, 8 and 15 of a 21-day cycle, followed by gemcitabine 1000 mg/m^2 as a 30-min IV infusion on days 1 and 8 of the cycle; there was no pre- or post-hydration. Patients randomized to arm B received cisplatin 100 mg/m^2 as a 2-h (intravenous) IV infusion on day 1 of a 21-day cycle, with pre-hydration and forced diuresis, followed by gemcitabine 1000 mg/m^2 as a 30-min IV infusion on days 1 and 8 of the cycle. Patients in each clinical site received the standard preparation regimen adopted in each participating institution, including an antiemetic agent. Granulocyte-colony stimulating factors (G-CSF) were allowed both prophylactically (according to the center policy) and therapeutically in the event of high grade neutropenia.

Before starting treatment, patients were assessed by complete physical examination, including neurological examination, electrocardiogram, disease evaluation by appropriate radiological techniques, (chest X-rays, CT scan of the chest, abdomen and brain, bone scan), complete blood cell count, serum chemistries and creatinine clearance. Patients were evaluated weekly prior to every infusion with laboratory tests and adverse event monitoring.

Adverse event severity was graded according to WHO Toxicity Criteria and doses were modified as defined in the protocol. In case of grade I nephrotoxicity, treatment was delayed, whereas in case of grade II nephrotoxicity, treatment was delayed and dose was reduced by 50% (Lipoplatin/cisplatin) and 15% (gemcitabine), with later increase upon creatinine level normalization; treatment was withdrawn in continuous renal dysfunction. Treatment was delayed in case of peripheral absolute granulocyte count $<1.5 \times 10^9$/l, or platelet count 75–100 $\times 10^9$/l. In case of peripheral absolute granulocyte count $<1.0 \times 10^9$/l, or platelet count 50–75 $\times 10^9$/l, treatment was delayed and dosages were reduced by 15%. Patients with grade IV toxicity were withdrawn from the study. Treatment delays were allowed for a maximum of 3 weeks.

Tumor measurements were assessed every 3 cycles, and treatment efficacy was evaluated according to the RECIST criteria [43]. Treatment was administered for 3 cycles, with 3 more cycles in the absence of disease progression.

2.5. Statistical considerations

The population for the efficacy analysis included all patients who completed at least 1 cycle of treatment. The population for the safety analysis was the "all treated population", which includes all patients that received at least one dose of study drug.

The primary end-point of the study was the objective response rate at 3 cycles, defined as the number of patients with tumor reduction by $\geq$30% or complete disappearance, according to the RECIST criteria. Death due to any cause or clinical deterioration was graded

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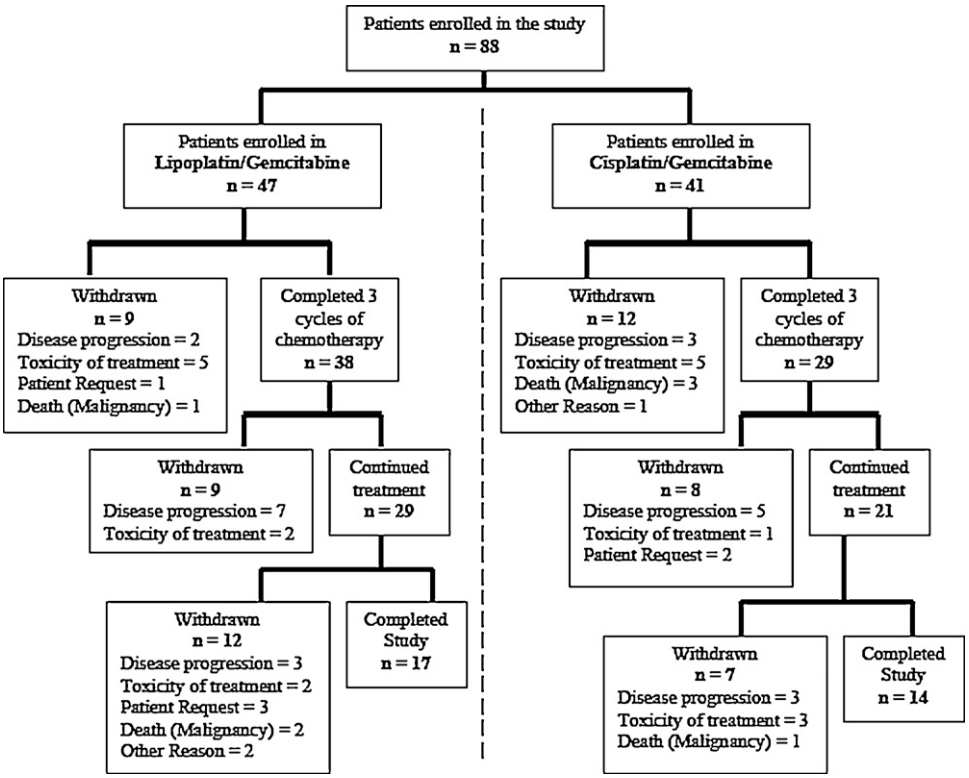

Fig. 1. Patient disposition.

as disease progression. The study was designed to test the null hypothesis of an ORR rate of 25% (p0), which is considered clinically unimportant, versus an alternative hypothesis of 45% ORR (p1). Considering a 5% type I error and a power of 80%, 43 patients were to be enrolled in each treatment arm.

Disease control rate was defined as the number of patients whose tumor did not progress on treatment. Progression-free survival and overall survival were calculated from day 1 of treatment, whereas duration of response was calculated from the date of radiological tumor measurements, showing complete or partial response. Survival curves were constructed using the Kaplan–Meier method.

Analysis of the toxicity and response results rendered percentages in each grade and disease status respectively. *p*-Values were calculated using the Pearson's Chi-square test on the basis of both patient count and infusion count applying the conventional statistical significance level of 0.05.

3. Results

3.1. Patient demographics

Following screening, a total of 88 patients, meeting the initial eligibility criteria, were enrolled into the study (Fig. 1). Patient demographic and other baseline characteristics are summarized in Table 1. The median number of cycles of chemotherapy received in both arms was 4 (range 1–6). Approximately 81% versus 71% of patients completed 3 cycles, while 32% versus 34% of patients completed 6 cycles of chemotherapy for arm A and arm B, respectively.

3.2. Efficacy

All patients who completed at least 1 cycle of treatment were included in the efficacy analysis. Response to treatment is summarized in Table 2. There were no complete responses. Partial response after 3 cycles was observed in 13 (31.7%) and 10 (25.6%) patients of arms A and B, respectively. Stable disease on the other hand was achieved in 16 (39%) patients in the LipoGem arm compared to 12 (30.8%) patients in the CisGem arm. DCR was 71% and 59% for arm A and arm B, respectively. Using the Pearson's Chi-square test, the *p*-value for the response rate was calculated to be 0.411; this is not a statistically significant *p*-value; a statistically significant difference in response rate between the two arms is expected to arise from an ongoing randomized Phase III study using the same treatment schedule.

Table 3 shows differences to response among NSCLC histological subtypes. It is interesting to note, despite the small number of patients analyzed in this comparative phase II study, that there is an indication that the Lipoplatin/gemcitabine treatment has a much higher response rate in adenocarcinomas (16.7% PD in LipoGem compared to 45.8% in CisGem) whereas in squamous cell carcinomas the Lipoplatin/gemcitabine treatment gave 46.1% PD compared to 37.5% PD in cisplatin/gemcitabine treatment.

Preliminary survival data were available from 23 patients from the LipoGem and 21 patients from the CisGem groups. The Kaplan–Meier OS and PFS curves are shown in Figs. 2 and 3. In OS an average of 51 weeks versus 43 weeks was recorded showing an 8-week higher average OS for LipoGem. Concerning PFS an average of 30 weeks versus 26 weeks was recorded. Thus, Lipoplatin appear to have a better efficacy compared to cisplatin delaying disease progression and prolonging survival when combined with gemcitabine as first line treatment against NSCLC.

3.3. Safety

All patients who received at least one drug infusion were included in the safety analysis. Treatment with LipoGem was well tolerated with much lower grade III/IV toxicities compared to the CisGem arm. Table 4 shows details of the incidence of treatment-

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Table 1
Patient demographics.

Parameter	Lipoplatin–gemcitabine	Cisplatin–gemcitabine
No. of Patients(n)	47	41
Male/female	45/2	33/8
Median age [years (range)]	64 (49–83)	66 (52–77)
Histological type [patients (%)]		
Adenocarcinoma	21 (45)	24 (59)
Squamous cell carcinoma	15 (32)	10 (24)
Large cell carcinoma	1 (2)	7 (17)
Low-differentiated NSCLC	10 (21)	0 (0)
Disease stage [patients (%)]		
I–IIIA (inoperable)	1 (2)	7 (17)
IIIB	15 (30)	7 (17)
IV	32 (68)	27 (66)
ECOG performance status [patients (%)]		
0	27 (57)	24 (59)
1	20 (43)	16 (39)
2	0 (0)	1 (2)
No. of metastatic sites (%)		
Median	1	1
0	16 (34)	14 (34)
1	11 (23)	15 (36)
2	6 (13)	8 (20)
3	4 (9)	2 (5)
4 or more	10 (21)	2 (5)
Previous treatments [patients (%)]		
Radiotherapy	9 (19)	4 (10)
Surgery	10 (21)	3 (7)
Radiotherapy and surgery [patients (%)]	2 (4)	3 (7)

NSCLC: non-small cell lung cancer; ECOG: Eastern Cooperative Oncology Group.

related adverse events for LipoGem ($n = 47$) versus the CisGem arm ($n = 41$) treated patients according to WHO.

The most frequent adverse events observed in arm A were grades I and II myelotoxicity; the majority of these toxicities, with the exception of anaemia, was observed in single infusions. There were no cases of febrile neutropenia. The only grade IV adverse event in LipoGem was a case neutropenia after a single infusion (1 patient, 2%) compared to 5 patients (12%) in the Cis/Gem arm. Neutropenia grade III was reported in 9% of patients in arm A versus 17% in arm B; Similarly, thrombocytopenia grade III was reported in 9% of patients in arm A versus 12% in arm B; neutropenia grade IV was 0% versus 10%, respectively.

Mild elevation of serum creatinine levels, graded as grade I nephrotoxicity, occurred in 38% of patients in arm A (LipoGem) versus 44% in arm B (Cis/Gem), mostly in single infusions. Grade II nephrotoxicity occurred in 6% versus 12% of patients; finally, grade III nephrotoxicity, severe enough to require hemodialysis in certain cases, was reported in 5% of patients in the CisGem arm. None of the patients in the LipoGem arm developed grade III nephrotoxicity. Mild neurotoxicity was reported in 13% of patients for arm A, whereas in arm B reported neurotoxocity grades II and III were 2% and 5%, respectively. Grades I–III gastrointestinal toxicity (nausea and vomiting) was reported in nearly 50% of the LipoGem patients versus 80% in the CisGem patients; it was

Table 2
Efficacy data of Lipoplatin + gemcitabine versus cisplatin + gemcitabine treatments.

Parameter	Arm A, LipoGem	Arm B, CisGem
No. of Patients (n)	47	41
Evaluable (%)	41 (87)[a]	39 (95) [a]
Non-evaluable (%)	6 (13)[b]	2 (5) [b]
Complete response	0 (0%)	0 (0%)
Partial response	13 (31.7%)	10 (25.6%)
Objective response rate [% (95% CI)]	13 (31.7%) [21.5–51.6]	10 (25.6%) [13.8–42.6]
Stable disease	16 (39%)	12 (30.8%)
Disease control rate [% (95% CI)]	29 (70.7%) [56.5–84.9]	22 (56.4%) [43.2–74.7]
Progressive disease	12 (29.3%)	17 (43.6%)
Median PFS [months (range)]	– (0.7–16.8+)[c]	– (0.2–9.8+)[c]
Median duration of response [months (range)]	– (2.8–14.8+)[d]	– (2.1–10.4+)[d]
CI 95% for PFS	6	6
Median OS [months (range)]	– (1.3–17.0+)[e]	– (1.0–16.5+)[e]
CI 95% for OS	8	10
1-year survival	30%	24%

CI: confidence interval; PFS: progression-free survival; OS: overall survival.
[a] Patients (n = 41) completed at least 3 cycles of treatment.
[b] Patients did not complete at least 1 cycle of treatment due to allergy or nephrotoxicity.
[c] Median progression-free survival has not been reached.
[d] Median duration of response has not been reached.
[e] Median overall survival duration has not been reached.

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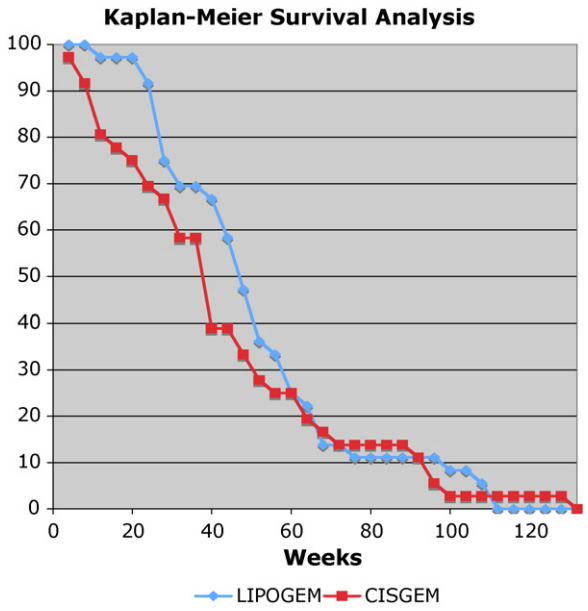

Fig. 2. Kaplan–Meier survival analysis (survival is shown in weeks). The average survival of 40 weeks in the Lipoplatin–gemcitabine arm versus 33.4 weeks in the cisplatin–gemcitabine arm was determined.

mainly grade I in arm A and responded well to antiemetic medications.

Approximately 570 infusions were given totally in the LipoGem arm and 310 in the CisGem arm (the ratio expected is 3:2 because of treatment schedule but the actual total number of infusion ratio is slightly different because more patients completed the intended cycles in the LipoGem arm compared to CisGem arm and because there were small differences in number of patients per arm). When the toxicities for each infusion were taken into consideration, statistically important differences between the two arms were obtained for nephrotoxicity (p-value < 0.001) and leukopenia (p-value = 0.009) and nearly significant for thrombocytopenia (p-value = 0.065), all favoring Lipoplatin (Table 3).

For instance, out of 569 measurements of serum creatinine, 486 were of grade 0 (85.4%) in arm A compared to 168 of 224 (75%) grade 0 in arm B. Grade I was 13% versus 19.6%, grade II was 1.4% versus 4.5%, and grade III was 0.2% versus 0.9% in arms A and B, respectively. The p-value was less than 0.001 showing statistically significant reduction of nephrotoxicity after replacement of cisplatin by Lipoplatin in its combination with gemcitabine (Table 5). A statistically significant but small reduction in leukopenia (8.2 versus 12.7%) is observed between arms A and B (p-value = 0.009). Thrombocytopenia of any grade was measured in 17.1% in LipoGem versus 23.5% in CisGem arms. The latter constitutes a significant finding if one considers that the main myelotoxic effect of the cisplatin–gemcitabine combination, i.e. thrombocytopenia, is reduced by Lipoplatin–gembitabine combination, an additional advantage of the liposomal formulation of cisplatin.

There were three serious allergic reactions during the first Lipoplatin infusion; mild hypersensitivity reactions, established as skin erythema, were observed in 4 out of the 47 patients, in single infusions, with no need for treatment discontinuation. The majority of the other adverse events, namely asthenia, anorexia and fever, was more frequent and more severe in the CisGem arm.

Table 3
Response to treatment in relation to histological type.

Histological type		Arm A (LipoGem) Patients, *n* (%)	Arm B (CisGem) Patients, *n* (%)
Adenocarcinoma	N	**18** (**100**%)	**24** (**100**%)
	PR	8 (44.4%)	6 (25.0%)
	SD	7 (38.9%)	7 (29.2%)
	PD	3 (16.7%)	11 (45.8%)
Squamous Cell Carcinoma	N	**13** (**100**%)	**8** (**100**%)
	PR	2 (15.4%)	2 (25.0%)
	SD	5 (38.5%)	3 (37.5%)
	PD	6 (46.1%)	3 (37.5%)
Undifferentiated NSCLC	N	**9** (**100**%)	**6** (**100**%)
	PR	2 (22.2%)	2 (33.4%)
	SD	4 (44.5%)	2 (33.3%)
	PD	3 (33.3%)	2 (33.3%)
Other Type	N	**1** (**100**%)	**1** (**100**%)
	PR	1 (100%)	0 (0%)
	SD	0 (0%)	0 (0%)
	PD	0 (0%)	1 (100%)

PR = partial response, SD = stable disease, PD = progressive disease, N/E = non-evaluable.

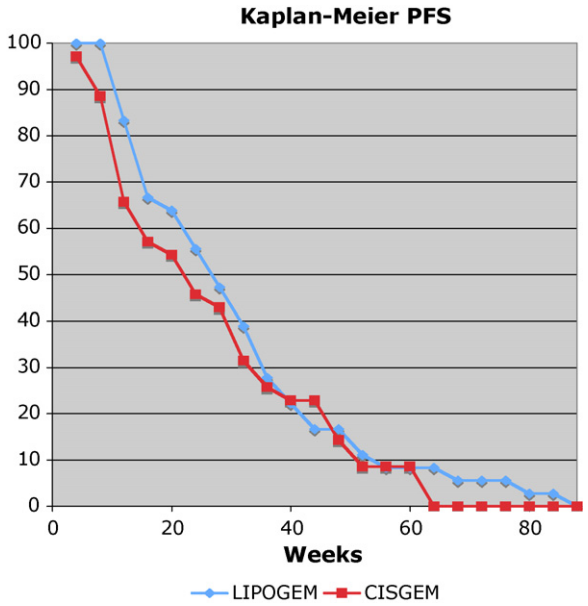

Fig. 3. Kaplan–Meier PFS curve.

4. Discussion

Lipoplatin, a liposomal formulation of cisplatin, was developed in order to reduce the systemic toxicity of cisplatin, while simultaneously improving the targeting of the drug to the primary tumor and metastases, by enhancing the circulation time in body fluids and tissues.

Acquired resistance to chemotherapy is a major hurdle in previously treated patients and the reason for the low response in second-line treatment. The major factor of resistance appears to be linked with transport of the chemotherapy drug across the cell membrane barrier. In this capacity, Lipoplatin, suggested to enter by direct fusion with the cell membrane of the tumor cell rather than the Ctr1 transporter as cisplatin, was proposed to have applications in cisplatin resistant tumors [44].

Human studies [45] have shown an astonishing targeting of tumors and metastases from an accumulation in total platinum in cancer tissue compared to adjacent normal tissue; in that study patients received an infusion of 100 mg/m^2 Lipoplatin 1 day before prescheduled surgery and blinded specimens obtained during surgery were analyzed for levels of platinum. The method was designed to differentiate between platinum trapped in tissue and platinum that had entered the tissue cells and reacted with macro-

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Table 4
Incidence of treatment-related adverse events for Lipoplatin–gemcitabine (ITT population) number of patients (n) = 47 versus the cisplatin–gemcitabine (ITT population) number of patients (n) = 41.

WHO-TC category term	LipoGem grade 1, n (%)	CisGem grade 1, n (%)	LipoGem grade 2, n (%)	CisGem grade 2, n (%)	LipoGem grade 3, n (%)	CisGem grade 3, n (%)	LipoGem grade 4, n (%)	CisGem grade 4, n (%)
Anaemia	23 (49)	23 (56)	20 (43)	14 (34)	1 (2)	4 (10)	0 (0)	0 (0)
Leukopenia	19 (40)	7 (17)	4 (9)	9 (22)	4 (9)	3 (7)	0 (0)	4 (10)
Neutropenia	11 (23)	4 (10)	11 (23)	9 (22)	4 (9)	7 (17)	1 (2)	5 (12)
Thrombocytopenia	20 (43)	18 (44)	6 (13)	5 (12)	4 (9)	5 (12)	0 (0)	4 (10)
Creatinine	18 (38)	18 (44)	3 (6)	5 (12)	0 (0)	2 (5)	0 (0)	0 (0)
Transaminases/bilirubin	12 (26)	10 (24)	9 (19)	11 (27)	2 (4)	6 (15)	0 (0)	1 (2)
Nausea/vomiting	18 (38)	10 (24)	4 (9)	18 (44)	1 (2)	5 (12)	0 (0)	0 (0)
Infection	11 (23)	2 (5)	0 (0)	2 (5)	1 (2)	0 (0)	0 (0)	0 (0)
Fever of unknown origin	9 (19)	7 (17)	6 (13)	3 (7)	0 (0)	1 (2)	0 (0)	0 (0)
Allergy	4 (9)	1 (2)	3 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Alopecia	5 (11)	8 (20)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
Sensory/motor	6 (13)	2 (5)	0 (0)	1 (2)	0 (0)	2 (5)	0 (0)	0 (0)
Asthenia	18 (38)	14 (34)	14 (30)	12 (29)	2 (4)	7 (17)	0 (0)	0 (0)
Anorexia	21 (45)	13 (32)	8 (17)	11 (27)	1 (2)	6 (15)	0 (0)	0 (0)
Metallic taste	2 (4)		0 (0)		0 (0)		0 (0)	

molecules (proteins, DNA, RNA and others). The study showed that the highest platinum levels were attained in gastric cancer specimens, presumably due to their high vascularization, suggesting very successful targeting of this cancer using this specific liposome nanoparticle technology. This observation along with the mechanism of targeting that involves extravasation through the endothelium of the tumors that bears tiny "holes" and allows the passage of the long-circulating Lipoplatin nanoparticles led to the proposal that Lipoplatin is both a chemotherapy and an antiangiogenesis drug [44]. This proposal was further supported from animal studies showing that systemic injection of a beta-galactosidase "blue gene" plasmid wrapped up in liposomes having the same shell structure as Lipoplatin to SCID mice bearing MCF-7 human breast cancer resulted in the preferential staining of the tumors and of the endothelium of tumor vasculature [44]. The mechanism(s) for the higher accumulation of Lipoplatin™ in tumor tissue compared to normal tissue, results in an overall 10–400-fold higher tumor cell uptake. The ability of Lipoplatin™ to target primary tumors and metastases and to cause a greater damage to tumor tissue compared to normal tissue contributes to its therapeutic efficacy. In this respect, Lipoplatin emerges as a very promising drug in the arsenal of chemotherapeutics.

In the current study, Lipoplatin 120 mg/m^2 (days 1, 8, 15 in a 21-day cycle) or cisplatin 100 mg/m^2 (day 1) was co-administered with gemcitabine 1000 mg/m^2 (days 1 and 8 of the cycle) in stage IIIb/IV NSCLC patients. Primary end-point of the study was ORR, secondary end-points were DCR, PFS, duration of response and OS. Although the final efficacy data are pending, initial results are promising, with 37% ORR and 71% DCR versus 28% ORR and 59% DCR for arms A and B, respectively. The results obtained in the present study

Table 5
p-Values of toxicities based on total count of infusions.

Grade		Arm	
		Arm A, LipoGem infusion number (%)	Arm B, CisGem infusion number (%)
I	Nephrotoxicity (p-value <0.001)	74 (13)	44 (19.6)
II		8 (1.4)	10 (4.5)
III		1 (0.2)	2 (0.9)
IV		0 (0)	0 (0)
Total		83/569 (**14.6**)	56/224 (**25**)
I	Leukopenia (p-value = 0.009)	33 (5.9)	17 (5.7)
II		10 (1.8)	15 (5)
III		3 (0.5)	3 (1)
IV		0 (0)	3 (1)
Total		46/558 (**8.2**)	38/300 (**12.7**)
I	Thrombocytopenia (p-value = 0.065)	77 (14.3)	55 (18)
II		8 (1.5)	9 (2.9)
III		6 (1.1)	4 (1.3)
IV		1 (0.2)	4 (1.3)
Total		92/537 (**17.1**)	72/306 (**23.5**)
I	Anaemia (p-value = 0.699)	354 (64.5)	192 (62.1)
II		52 (9.5)	36 (11.7)
III		2 (0.4)	2 (0.6)
IV		0 (0)	0 (0)
Total		408/549 (74.3)	203/309 (74.4)
I	Nausea & Vomiting (p-value < 0.001) numbers denote patients, not infusions	18 (38)	10 (24)
II		4 (9)	18 (44)
III		1 (2)	5 (12)
IV		0 (0)	0 (0)

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with Lipoplatin/gemcitabine compare favorably to those obtained with cisplatin/gemcitabine, and the latter combination has yielded efficacy and toxicity figures not inferior to the already published studies in the literature evaluating this combination in advanced NSCLC [46,47,48]

The commonest toxicities observed were grades I and II myelotoxicity, nevertheless significant grades III and IV myelotoxicities were observed in the cisplatin/gemcitabine combination treatment. These toxicities occurred mostly in single infusions and responded well to hemopoietic factors. Moreover, it must be noted that, in this study, Lipoplatin/cisplatin is combined with gemcitabine, a known myelotoxic agent. Gastrointestinal toxicity was observed to be more frequent and more severe in arm B patients (grades II and III 11% in arm A versus 56% in arm B).

Hypersensitivity reactions were observed in seven LipoGem patients. In three of them, it occurred as serious allergic reaction in the first infusion. In another patient it was associated with increased speed of infusion. In all cases, reactions resolved with no immediate threat to life, while no hospitalization was required.

Grades I–II nephrotoxicity was observed in 44% of arm A patients, mostly in single infusions, versus 56% in arm B. There was no dose reduction due to nephrotoxicity. Three patients in arm A developed grade II nephrotoxicity, two of them after their first treatment; comparatively, five grade II and two grade III nephrotoxicity cases were observed in arm B. All patients recovered well with adequate hydration. Neurotoxicity, a major side effect of cisplatin, was observed in a limited number of patients and was milder (grade I) in arm A. None of the cases required treatment discontinuation.

5. Conclusion

Overall, Lipoplatin was shown to have lower toxicity, mainly nephrotoxicity, as well as higher efficacy than cisplatin, when combined with gemcitabine in advanced NSCLC. There were no associated deaths, or life-threatening adverse events. Particularly relevant is that Lipoplatin is administered without pre- or post-hydration, on an outpatients basis. The higher response, although statistically insignificant because of the small patient sample, as well as the reduced overall toxicity are proposed to arise from the ability of the Lipoplatin nanoparticles to preferentially attack tumor cell and tumor cell vasculature compared to normal tissue. This combination and treatment schedule is being further investigated in a Phase III study.

Conflict of interest

The authors have nothing to declare.

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