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First Safety and Response Results of a Randomized Phase III Study with Liposomal Platin in the Treatment of Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN)

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Abstract. *Background: Cisplatin is one of the most active chemotherapeutic agents used in the treatment of advanced squamous cell carcinoma of the head and neck (SCCHN). However, its clinical efficacy is limited by its renal and hematotoxicity profile. In a randomized, multicenter phase III trial, we replaced conventional cisplatin by a liposomal formulation of cisplatin (lipoplatin) and compared the safety and efficacy profiles of patients in the two treatment arms. Patients and Methods: Main inclusion criteria were: histologically confirmed SCCHN, age between 18-75 years with sufficient renal function. Main endpoints for this interims analysis were hemato- and nephrotoxicity. First response data were collected. Results: Forty-six patients were evaluable for outcome and toxicity. Grade III and IV hematotoxicity was more frequent in the cisplatin arm (31.7% vs. 12%), with grade IV leucopenia occurring in 22.2%. However, 16% of the patients in that treatment arm experienced grade III anemia compared to only 9.5% treated with the cisplatin regimen. A total 4% of the patients in the lipoplatin arm developed grade IV neuropathy, whereas in the cisplatin arm, 19% developed grade III neuropathy and none developed grade IV. The renal toxicity profile of both drugs also showed marked differences. In the cisplatin arm, 23.8% of patients suffered grade III toxicity. In contrast, no grade III or IV renal toxicity occurred in patients treated with lipoplatin. The efficacy results showed 38.8% objective partial remission in the cisplatin arm vs. 19% in the lipoplatin arm. However 64% of the patients achieved stable disease while being treated with lipoplatin/5-fluorouracil (5-FU), vs. 50% in the cisplatin/5-FU arm. Conclusion: Liposomal platin seems to reduce both the renal and hematological toxicity to a clinically relevant extent as compared to conventional cisplatin. The clinical benefit rate is similar for both regimens.*

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Over the last 10 years, overall survival rates for patients with head and neck cancers have improved as has the quality of life (1). Despite aggressive early therapy with surgery and radiation, resistant squamous cell carcinoma of the head and neck (SCCHN) often occurs leaving chemotherapy the only option.

Cisplatin is still the reference drug in the induction chemotherapy setting when used in combination with 5-fluorouracil (5-FU). However, its clinical use is limited by its causing peripheral neuropathy, renal and hematological toxicity, manifesting themselves at increasing cumulative doses (2).

The liposomal formulation of cisplatin, lipoplatin™ , was created by capturing the cisplatin molecule within a layor of anionic lipid dipalmityl phosphatidyl glycerol (DPPG). The application of liposomes as drug carriers offers the possibility to manipulate the pharmacokinetics of drugs and to improve their efficacy and reduce toxicity (3, 4). Animal studies have shown, that the leaky vasculature of solid tumors facillitates the extravasation of these nanoparticles (110 nm) and their preferential fusion with the cell membranes of tumor cells (5). Through this mechanism, both the systemic release of cisplatin and the toxic side-effects are reduced (6).

To test this in a clinical setting we designed a randomized, multicenter phase III trial of SCCHN, in which conventional cisplatin or the liposomal formulation of cisplatin (lipoplatin) was used in combination with 5-FU, and compared efficacy and the safety profiles of both treatment arms.

Patients and Methods

This study was approved by the Institutional Review Board and all patients signed informed consent forms.

Patients. Only patients with histologically confirmed SCCHN (primary metastatic or patients with relapsed/progressive disease) with at least one measurable bidimensional lesion, between the age of 18-75 years, a performance status of at least ECOG 3, an adequate bone marrow function (a peripheral absolute leukocyte count of at least 2,500/mm^3 and platelet count of at least 100,000/mm^3) and an adequate liver function, with a sufficient renal function (defined as creatinine clearance >50 ml/min) were included in the study. Creatinine clearance (CrCl) was estimated by the method of Trollfors *et al*. (7). Exclusion criteria included progression during 100 mg/m^2 per day cisplatin-based chemotherapy, no progressive disease after chemotherapy or radiochemotherapy, less than 3 weeks since prior surgery, pregnancy, active/unstable ischemic heart disease, Hepatitis B or C and of course the use of nonstudy cancer therapy.

Treatment. After stratification (criteria: primary metastatic disease, recurrent or progressive SCCHN, prior chemotherapy/no prior chemotherapy, prior cisplatin-based chemo-therapy/prior non cisplatin-based chemotherapy and center), patients were randomized between the following arms: Arm A: patients received 100 mg/m^2/day lipoplatin 4 h intravenous infusion (day 1,8,15) plus 1000 mg/m^2/day 5-FU (day 1-5 continuous infusion) every three weeks for six cycles; Arm B: patients received 100 mg/m^2/day cisplatin with pre- and posthydration (day 1) plus 1000 mg/m^2/day 5-FU (day 1-5 continuous infusion) every three weeks for six cycles. A dose reduction of cisplatin occurred from 100 mg/m^2 to 70 mg/m^2 when the creatinine clearance fell between 99 ml/min and 70 ml/min, leukopenia <500/μl during the last cycle, neutropenic fever/infection during last cycle or thrombopenia <50.000/μl during the last treatment cycle. Cisplatin was reduced to 50 mg/m^2 when the creatinine clearance fell between 69 ml/min and 50 ml/min or mucositis CTC grade 4 occurred. 5-FU was reduced in dose from 1000 mg/m^2/day to 500 mg/m^2/day when severe hand and foot syndrome or mucositis CTC grade 4 occurred. No dose reductions of lipoplatin were performed. Toxicity was evaluated before and after every cycle according to CTC, while response was evaluated by computer tomography scans after every two cycles. Main endpoints for this interims analysis were hemato-, neuro- and nephrotoxicity and efficacy.

Results

To date, a total of 46 patients were evaluable after at least 2 cycles in both arms: 25 patients in the lipoplatin and 21 patients in the conventional cisplatin arm respectively. The demographic characteristics are shown in Table I. Both arms were similar in age and performance status, with the majority of patients (87%) being male (n=40) *versus* 6 (13%) women. Most patients (72% *vs*. 71.4%, respectively) had advanced stage cancer, with UICC Stage IV C at study entry.

Patients treated with the lipoplatin combination received a mean number of 4.2 cycles of chemotherapy as compared to 3.7 cycles in the cisplatin-based regimen. One patient died in cycle 1 of the lipoplatin arm, while 3 patients died and another 3 were lost to follow-up during the first cycle of the conventional cisplatin arm. None of the deaths were directly chemotherapy-related. Seven patients had to stop cisplatin therapy due to severe toxicity as compared to one patient in the lipoplatin treatment arm. Hematotoxicity, neurotoxicity, mucositis and renal toxicity were the major confounding side-effects.

Table I. *Patient characteristics*.

	Lipoplatin	Cisplatin
Total number of patients	25	21
Total cycles applied	106	77
Mean cycles applied	4.2 (2-6)	3.7(2-6)
Age (years)(mean)	56.2 (55-65)	58.1 (53-63)
No. patients (%)		
Gender		
Female	4 (16%)	2 (9.5%)
Male	21 (84%)	19 (90.5%)
ECOG Performance Status		
1	16 (64%)	13 (62%)
2	7 (28%)	6 (33.3%)
3	2 (8%)	2 (9.5%)
Primary metastatic disease	4 (16%)	4 (19%)
Relapsed or progressive disease after surgery and/or radio/chemotherapy	21 (84%)	17 (81%)
UICC Stage at Study entry		
IV A	2 (8%)	2 (9.5%)
IV B	5 (20%)	4 (19%)
IV C	18 (72%)	15 (71.4%)
Prior chemotherapy	15 (60%)	10 (55.6%)
Prior chemotherapy cisplatin based	10 (40%)	7 (38.9%)
Histology		
Squamous cell carcinoma	24 (96%)	19 (90,5%)
Adenocarcinoma	1 (4%)	2 (9.5%)
Completed study with 6 cycles	10 (40%)	6 (33.3%)

Severe hematotoxicity was more frequent in the cisplatin arm, with grade III and IV toxicity occurring in 31.7% of the patients treated with the cisplatin-based regimen *vs*. 12% in the lipoplatin arm (Table II). Grade IV leucopenia occurred in 22.2% of the patients treated with cisplatin, whereas in the lipoplatin arm, 0% grade IV leukopenia occurred. However, 16% of the patients in that treatment arm experienced grade III anemia compared to only 9.5% treated with the cisplatin regimen. No grade III or IV thrombopenia occurred in either of the treatment arms.

A total of 67% of the patients treated with the cisplatin regimen experienced grade I and II neuropathy compared to only 27% in the lipoplatin arm (Table III). However, 4% of the patients in the lipoplatin arm developed grade IV neuropathy, whereas in the cisplatin arm 19% developed grade III neuropathy and none developed grade IV.

More patients developed severe mucositis in the cisplatin-based regimen than in the lipoplatin treatment (Table III). Of

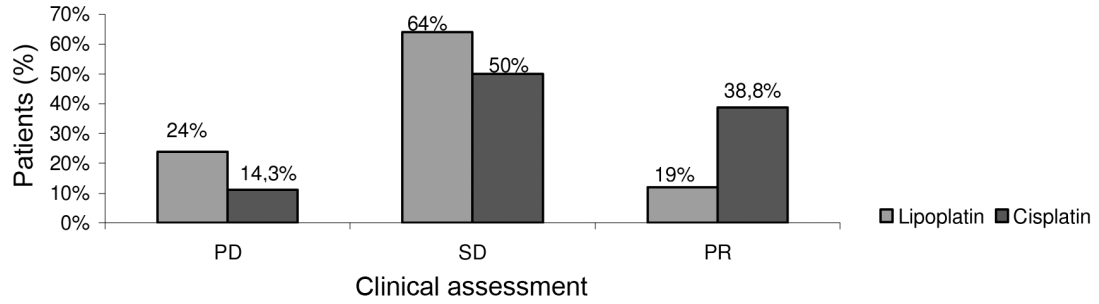

Figure 1. *Response rates in %. PD: progressive disease; SD:stable disease; PR: partial remission for cisplatin (n=21) and lipoplatin (n=25).*

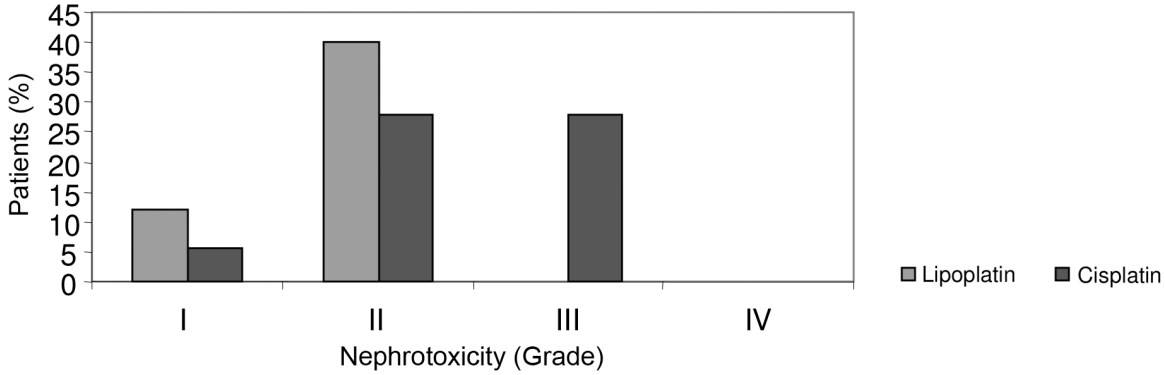

Figure 2. *Decrease of creatinin clearance (ml/min) after treatment with cisplatin (n=21) and lipoplatin (n=25). Grade I: 75-99 ml/min; grade II: 50-74 ml/min; grade III <50 ml/min; grade IV: dialysis.*

Table II. *Hematological toxicities (CTC) for cisplatin/5FU regimen (n=21) vs. lipoplatin/5FU regimen (n=25).*

Grade	I		II		III		IV	
% Patients	Cisplatin	Lipoplatin	Cisplatin	Lipoplatin	Cisplatin	Lipoplatin	Cisplatin	Lipoplatin
WBC	33.3	16.0	22.2	7.0	9.5	0.0	22.2	0.0
Platelets	19.0	8.0	14.3	0.0	4.8	0.0	0.0	0.0
Hemoglobin	33.3	20.0	38.9	16.0	9.5	16.0	0.0	0.0

Table III. *Non hematological ttoxicities (CTC) for cisplatin/5FU regimen (n=21) vs. lipoplatin/5FU regimen (n=25).*

Grade	I		II		III		IV	
(%) Patients	Cisplatin	Lipoplatin	Cisplatin	Lipoplatin	Cisplatin	Lipoplatin	Cisplatin	Lipoplatin
Nausea	4.8	8.0	27.8	16.0	28.6	8.0	9.5	0.0
Mucositis	4.8	8.0	22.0	4.0	19.0	4.0	14.3	4.0
Diarrhea	9.5	0.0	9.5	4.0	19.0	4.0	0.0	0.0
Infection	0.0	0.0	9.5	12.0	28.6	28.0	14.3	0.0
Allergic reaction	0.0	0.0	0.0	8.0	0.0	0.0	0.0	4.0
Renal	9.5	12.0	28.6	40.0	23.8	0.0	0.0	0.0
Neuropathy	33.3	27.0	33.3	0.0	19.0	0.0	0.0	4.0

the patients treated with cisplatin 33.3% suffered grade III or IV mucositis with mostly hospitalization necessary compared to only 8% in the lipoplatin treatment arm.

The renal toxicity profile of both drugs also showed marked differences. In the cisplatin arm, 23.8% of the treated patients suffered a significant reduction in kidney function, with a decrease in creatinine clearance below 50 ml/min (Table III). Three patients suffered acute renal insufficiency, however not needing dialysis. In contrast, no grade III or IV renal toxicity occurred in patients treated with lipoplatin. However, 40% of these patients experienced toxicity grade II, with a decrease in creatinine clearance to a range between 50-74 ml/min.

The efficacy results showed 38.8% objective partial remission in the cisplatin arm *vs*. 19% in the lipoplatin arm. However, 64% of the patients achieved stable disease while being treated with lipoplatin/5-FU, compared to 50% of the patients in the cisplatin/5-FU arm. A total of 24% of the patients progressed while being treated with lipoplatin *vs*. 14.3% of these treated with cisplatin.

Discussion

This ongoing study has shown so far that the lipoplatin formulation reduces both the hematological and non hematological toxicity profiles of cisplatin to a clinically relevant extent when combined with 5-FU.

Renal toxicity is one of the major limiting factors of cisplatin in the palliative treatment of advanced SCCHN (8, 9). Compared to cisplatin, lipopatin showed a favourable profile in conserving renal function during treatment with no grade III or IV renal toxicity. However the authors feel, that the high percentage of renal toxicity associated with the cisplatin arm in this study, especially the three patients suffering acute renal failure, does not fully reflect the experience at our institution with this drug. It does, however, stress the importance of sufficient hydration in these patients and should never be underestimated.

Lipoplatin also showed a favourable hematological toxicity profile. Nearly one third of the patients treated with cisplatin developed grade III or IV haematological toxicities during treatment, with leucopenia (31.7%) and neutropenic fever (16.7%) being most frequent. In view of the high rate of severe mucositis in this group (33.3%), special caution is warranted.

One of most debilitating toxic side-effects and a great impingement on the quality of life of cisplatin-based chemotherapies is neuropathy. Lipoplatin seems to reduce neuro-toxicity profoundly. Grade I and II neuropathy was reduced by half in the lipoplatin-containing regimen. Even at the higher grades III and IV lipoplatin showed less than half the toxicity compared to that of cisplatin (4% *vs*. 19% respectively).

In view of the high rate of stable disease in the lipoplatin arm (64% *vs*. 50%), the clinical benefit rate (stable disease + partial remission) is similar for the cisplatin (88.5%) and lipoplatin combination (83%), even though there were more objective responses seen in the cisplatin arm.

Conclusion

Because patients with advanced SCCHN have an increased risk of renal toxicity due to poor hydration, the observed reduction of side-effects with lipoplatin can help to preserve the dose density of chemotherapy, and thereby efficacy, and to improve the quality of life of these patients.

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