

Cisplatin Administration at Outpatient Clinics is Safe Compared to the In-Patient Usual Protocol: Findings from a Comparative Study

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Abstract

Introduction: Cisplatin is widely used in thoracic oncology. Its main limiting adverse effect is renal toxicity. A huge intravenous hydration is known to deliver administration of high-dose cisplatin at out-patient (OP) clinic using a shorter intravenous hydration protocol. However, the safety of this strategy has never been investigated yet. Here, we aimed to provide a comparative study of creatinine clearance levels changes in OP compared to the standard in-patient protocol (IP).

Method: This is a retrospective study comparing two centers: one using the IP standard protocol and the other the OP. We used a general linear model for a confounder-adjusted assessment of the mean difference in creatinine clearance between the two groups.

Results: 227 patients were included (172 in IP and 55 in OP). Pre-cisplatin basal clearance levels were comparable between the two groups. Overall, we found neither clinically relevant nor statistically significant differences in clearance levels change between the two groups regarding each cisplatin cycle. In the multivariable analysis, we found no significant difference in clearance levels among the groups. We found a higher frequency of unexpected hospitalization in IP than in OP (18% vs. 33%; p=0.034) as well as a higher cisplatin dose reduction frequency (16% vs. 39%; p=0.002).

Conclusion: We showed that safe administration of high-dose cisplatin in outpatient clinic is feasible. Emphasize should be put on selection of eligible patients and on the mandatory oral hydration.

Keywords: Lung cancer; Cisplatin; Chemotherapy; Creatinine Clearance; Adverse event

Introduction

Cisplatin is the cornerstone of chemotherapy administered in first line treatment of metastatic and locally advanced stages as well as in an adjuvant setting for Non-Small Cell Lung Cancer (NSCLC) [1,2]. Cisplatin has significant toxicity profile with adverse effects such as neutropenia, anemia, peripheral neuropathy, ototoxicity, asthenia, acute and delayed nausea and vomiting, and nephrotoxicity.

Cisplatin is mainly eliminated in urine and concentrates in proximal tubules. Thus, cisplatin concentration may be fivefold higher in tubule epithelial cells than in blood and could therefore reach a toxic concentration in tubule while the simultaneous blood level remains low. In tubules, cisplatin may induce epithelial cell death which may raise an inflammatory reaction worsening the renal failure. Injuries may then expand to distal tubules and glomeruli.

Cisplatin induced nephrotoxicity is dose-dependent and dose-limiting. It is a frequent adverse event occurring in about one quarter of patients treated [3,4]. Huge hydration is known to decrease the cisplatin tubule concentration and thus, to prevent nephrotoxicity. This hydration is usually administered intravenously (as cisplatin may also induce nausea and vomiting) and compel to a 48-hours stay in hospital.

In response to increasing pressure on in-patient facilities as well as on the request of patients who prefer an outpatient delivery, some teams develop alternative processes for high dose cisplatin administration. Among those, one is to deliver a shorter intravenous hydration schedule enabling cisplatin administration in an outpatient clinic. However, to date, no study provided a comprehensive safety comparison of an inpatient (with shorter hydration) schedule versus the conventional outpatient schedule.

Accordingly, we decided to investigate whether administration of cisplatin at outpatient clinic was associated to toxic renal events compared to inpatient administration.

Method

Study design

This study is a retrospective two-arm uncontrolled cohort study. Two university thoracic oncology units were involved. Cisplatin was administered through conventional (in-patient) schedule in the first one (CHU Lyon Sud, Hospices Civils de Lyon, France) whereas cisplatin was delivered at outpatient clinic with a short hydration protocol in the second one (CHU Grenoble, France). This study was declared as an observational study to Lyon Hospital Ethic Committee.

Cases were identified through the hospital databases. Inclusion criteria were all patients initiating chemotherapy by cisplatin for lung cancer - irrespectively of the stage - between January 1st 2008 and December 31, 2010. Data were retrospectively collected in medical charts.

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The main outcome was the difference in the creatinine clearance level 3 weeks after the last cisplatin course. Secondary outcomes included difference in creatinine clearance level at each cisplatin course and 12 weeks after the last course.

In- and out-patient cisplatin delivery protocols

Patients in the in-patient (IP) protocol were administered with one litre of normal saline solution intravenously every 8 hours from day-0 until day-2. Cisplatin was administered at day-1 during a 2-hours intravenous infusion. Patients' diuresis was tightly monitored during the 48 h stay and a 20 mg furosemide intravenous injection was systemically administered if diuresis was under 1000 ml/8 h. Patients were discharged at day-2.

Patients in the outpatient (OP) protocol underwent a 2 litres normal saline infusion during 8 hours intravenously. Cisplatin was administered at a rate of 1 mg/min (resulting in a 2 to 3 hours infusion). Diuresis was monitored during the in-hospital stay but furosemide infusion was not systematically used. Patients were hosted in the morning and discharged in the afternoon. All were consistently informed of drinking at least 2 litres of water during the forthcoming 24 hours and sustaining an intake of at least 1.5 litres of water per day all other days. Written information was delivered. In addition, physicians systematically assessed concomitant medications and all drugs with potential renal toxicity were stopped if medically possible.

Cisplatin was delivered with a doublet drug according to standard of care and to the physician judgement. Moreover, the dose of cisplatin could differ between the different protocols from 75 mg/m² to 80 mg/m². Finally, the total planned cycle of chemotherapy could be different from a patient to another one; but in both centres, the usual procedure retains 4 courses. Hereafter, when we consider the last course, it means the last course of cisplatin delivered (whatever how many courses were planned).

Renal function assessment

In both centres, a serum creatinine dosage was mandatory before administering cisplatin chemotherapy. This dosage was performed the day before chemotherapy and was filed in medical chart. We also recorded the serum creatinine dosage 3 weeks and 12 weeks after the last course when available. We used the Cockcroft and Gault (CG) formula to calculate the creatinine clearance estimation [5]. Clearance was expressed in milliliter by minute.

Statistical analysis

For continuous variables, assumption of normal distribution was assessed by the one-sample Kolmogorov-Smirnov test. Continuous variable were described by their mean and standard deviation or, in case of skewed distributions, by their median and interquartile range. Uni-variate comparison of means between two independent groups was conducted by the Student t-test. For the comparison of the central tendency of non-normally distributed variables we used the Mann-Whitney U test. Categorical variables were expressed in percent. Comparison of categorical variables was performed using the Chi-squared test or the two-sided Fisher test as appropriate.

Multivariate analysis was performed at four time points: at first cycle, at last cycle, 3 weeks after the last, and 12 weeks after the last. The outcome used for this analysis was the difference between creatinine clairance in OP group minus IP group. Mean differences in clearance levels between the two study's groups were presented with their corresponding 98.75% confidence interval. This width was chosen to

emulate a Bonferroni correction of type one error considering the four evaluation time points (adjusted level of significance: 0.0125) [6]. Then, we used a general linear model. We selected variables with the highest potentially influence and/or those with a significant effect in uni-variate analysis. These variables were those included into the multivariate model to perform a confounder adjustment.

All statistical tests were conducted two-sided and a p-value <0.05 was considered to indicate statistical significance. Except for the primary study endpoint, no correction of P values was performed in the course of multiple testing; however, results of all performed tests were thoroughly reported, allowing for an informal adjustment for multiplicity while reviewing the data [7].

Statistical analyses were performed with the SPSS v19.0 software (IBM Corp, Armonk, NY, USA).

Results

Population

Two hundred and twenty seven patients were included in the study: 172 in the IP group and 55 in the OP group. Main characteristics of the two groups are shown in Table 1. There was a significant difference between the groups according to the doublet drug used: gemcitabine and vinorelbine were the preferred drugs in IP (46% and 38% respectively) while docetaxel was frequently used in OP (54%). With respect to cisplatin delivery, the median planned dose was significantly higher in IP than in OP (80 mg/m² (± 0) versus 75 (± 5), (p<10⁻⁴). Median number of delivered course of cisplatin (n=4) did not differ into the two groups. Finally, OP showed a significantly lower rate of patient with nephrotoxic concomitant drugs.

Serum creatinine clearance levels

Results of clearance of creatinine levels in both groups are reported in Table 2. Pre-cisplatin basal levels did not differ and were normally distributed. There was a small – but significant – difference favoring OP in creatinine clearance level at last course of cisplatin. Similar finding were found 12 weeks after the last course of cisplatin. However, we found no difference in serum creatinine clearance level 3 weeks after the last regimen of cisplatin (main objective) as well as for courses 2 to 6.

Multivariate analysis

The multivariate adjustment was computed with the following variables: tobacco status (ever vs never), doublet drug (vinorelbine/docetaxel/other), planned dose of cisplatin (60/75/80 mg/m²), and use of nephrotoxic drugs (Yes/No). Adjusted mean differences in clearance levels between the two study's groups (i.e. mean creatinine level in IP minus mean creatinine level in OP with the corresponding 98.75% CI) are shown in Figure 1. We found no significant difference across the two groups whatever the chemotherapy course considered. However, there was a non-significant trend favoring the OP delivery for last course as well as for 3 weeks and 12 weeks courses.

Clinical outcomes and objective response rate

Clinical outcomes related to cisplatin administration are reported in Table 3. There were significantly more events in IP arm than in OP. In the IP group, 39% patients experienced at least one cisplatin dose reduction compared to 16% in OP (P=0.002) and the difference remained significant when restricted to nephrotoxicity-related outcomes. We also found a higher proportion of unexpected or extended hospitalization in the IP group (33% versus 18% in OP group; P=0.034) although not

		Inpatient group (n=172)	Outpatient group (n=55)	P-value	Total (n=227)
Sex	Male	132 (77%)	42 (76%)	0.954	174 (77%)
Age	Mean in years (\pm SD)	57.3 (\pm 7.6)	57.8 (\pm 8.3)	0.655	57.4 (\pm 7.8)
Tobacco Status	Current smoker	91 (53%)	15 (31%)	0.005	106 (48%)
	Former and never smoker	80 (47%)	34 (69%)		114 (52%)
	Missing	1	6+		7
Patient's size	Mean in cm (\pm SD)	170 (\pm 9)	169 (\pm 6)	0.711	170 (\pm 8)
	Missing	1	1		2
Weight at diagnosis	Mean in Kg (\pm SD)	69 (\pm 13)	69 (\pm 11)	0.708	69 (\pm 13)
	Missing	3	5		8
	Adenocarcinoma	102 (60%)	30 (54%)	0.695	132 (58%)
Histologic subtype	Squamous cell carcinoma	40 (23%)	13 (24%)		53 (24%)
	Other	29 (17%)	12 (22%)		41 (18%)
	Missing	1			1
	Stage I to IIIA	27 (16%)	11 (20%)		38 (17%)
Disease stage	Stage IIIB and IV	144 (84%)	44 (80%)		188 (83%)
	Missing	1			1
	PS 0 to 1	159 (95%)	47 (94%)	0.547	206 (95%)
Performance status	PS 2	9 (5%)	3 (6%)		12 (5%)
	Missing	4	5		9
	Docetaxel	2 (1%)	30 (54%)	<0.0001	32 (14%)
Chemotherapy doublet drug	Gemcitabine	79 (46%)	19 (35%)		98 (43%)
	Pemetrexed	24 (14%)	5 (9%)		29 (13%)
	Vepeside	1 (1%)	-		1 (1%)
	Vinorelbine	65 (38%)	1 (2%)		66 (29%)
	Bevacizumab	10 (6%)	0		10 (4.4%)
	Scheme with day-8	142 (83%)	20 (36%)		162 (72%)
	Missing	1	-		1
Thoracic radiotherapy	Yes	37 (25%)	11 (22%)	0.702	48 (24%)
	Missing	22	5		27
Cisplatin planned delivery dose	Median in mg/m ² (\pm IQR) -	80 (\pm 0)	75 (\pm 5)	<0.0001	80 (\pm 5)
	Missing	7	3		10
Cisplatin delivered courses (n=226)	Median \pm IQR	4 (\pm 3)	4 (\pm 2)	0.065	4 (\pm 3)
	Missing				
Relevant comorbidities ^a	At least one	47 (27%)	12 (22%)	0.405	59 (26%)
	Missing	1			1
Concomitant use of nephrotoxic drugs ^b	At least one	34 (20%)	4 (7%)	0.03	38 (17%)
	Missing	1			1

Table 1: Main characteristics of the population included in the study.

Time points	Creatinine clearance (ml/min)				p value	
	Inpatient (IP)		Outpatient (OP)			
	N	Mean	N	Mean		
Cisplatin #1	171	89.6 \pm 25.6	55	88.9 \pm 17.6	0.859	
Cisplatin #2	156	83.6 \pm 25.5	51	90.0 \pm 20.8	0.107	
Cisplatin #3	125	81.8 \pm 31.5	35	85.8 \pm 19.1	0.465	
Cisplatin #4	91	79.3 \pm 26.1	29	86.8 \pm 20.3	0.159	
Cisplatin #5	46	78.6 \pm 29.8	5	88.4 \pm 23.4	0.480	
Cisplatin #6	31	72.4 \pm 33.9	3	73.9 \pm 6.5	0.942	
Last Cisplatin	171	76.8 \pm 26.0	55	83.3 \pm 18.2	0.044	
3 weeks after last	121	67.5 \pm 27.0	31	77.5 \pm 19.2	0.054	
Missing	50		24			
12 weeks after last	86	68.8 \pm 26.0	34	81.1 \pm 21.1	0.015	
Missing	85		21			

Table 2: Mean serum creatinine clearance in the two groups.

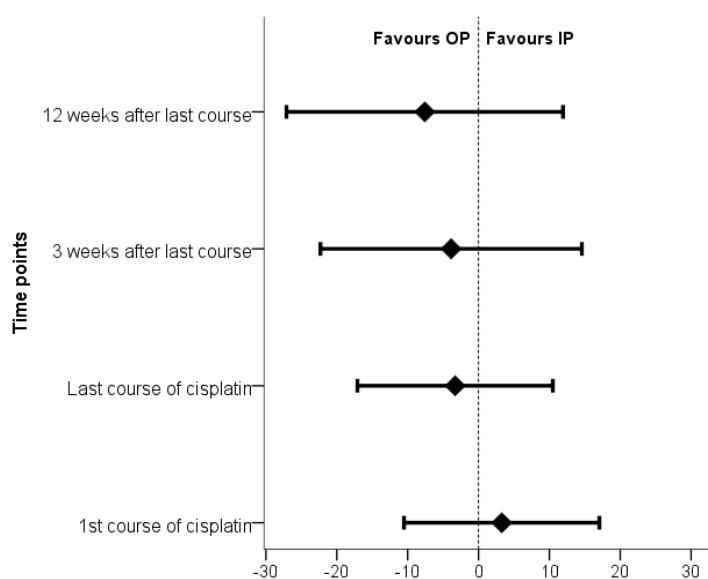


Figure 1: Difference in mean creatinine clearance between the two groups adjusted for doublet drug (Gemcitabine or pemetrexed or other/vinorelbine/docetaxel); planned cisplatin dose (60/75/80); smoking (never/ever); use of concomitant nephrotoxic drug (yes/no). Interval lines indicate the 98.75% confidence interval. Dotted line indicates the zero level (no difference).

	Inpatient (n=171)	Outpatient (n=55)	Total (n=227)	P value
At least one unexpected or extended hospitalization	57 (33%)	10 (18%)	67 (30%)	0.034
<i>Because of nephrotoxicity</i>	10 (6%)	4 (7%)	4 (6%)	0.749
At least one delayed or cancelled cisplatin course	50 (29%)	19 (35%)	69 (30%)	0.442
<i>Because of nephrotoxicity</i>	4 (2%)	4 (7%)	8 (4%)	0.1
At least one dose reduction in cisplatin	67 (39%)	9 (16%)	76 (33%)	0.002
<i>Because of nephrotoxicity</i>	32 (19%)	4 (7%)	36 (16%)	0.045
Unexpected cisplatin regimen final stop	85 (49%)	26 (47%)	111 (49%)	0.877
<i>Because of nephrotoxicity</i>	26 (15%)	5 (9%)	31 (14%)	0.257
At least one nausea and vomiting ≥ CTC grade 2	23 (13%)	7 (13%)	30 (13%)	0.902

Table 3: Chemotherapy-related clinical outcomes in the two groups.

associated to nephrotoxicity.

Discussion

In this study, we showed that administering cisplatin in an outpatient clinic and with a short hydration protocol is not associated to creatinine clearance worsening compared to the conventional inpatient protocol.

Our results are consistent with those previously reported in the field. Indeed, some teams developed alternative protocol for high dose cisplatin administration at the outpatient clinic. One alternative is to deliver a short hydration schedule enabling administration in one day. Six teams have previously reported their own experience and showed that this approach seemed feasible and safe [8-13]. Only one retrospectively compared creatinine clearance in 57 in-patients and 88 out-patients with high-dose cisplatin. This study found a non-significant higher mean percentage increase of creatinine (+13%) in the in-patient group [13]. All other were retrospective and mono-centric in Japan (n=22) [10], France (n=357) [9], Italy (n=21 and 107) [8,11] and USA (n=30) [12]. All had a focus on renal function and found a favourable safety profile for the outpatient administration protocol. In addition,

an Australian team initiated a prospective trial comparing outpatient to inpatient cisplatin delivery in a self-cross-over design (each patient received both schedule, sequence was randomly allocated). Main outcome was patient preference for in- or outpatient schedule. Authors found no significant difference in adverse effect rates (without focus on renal toxicity) nor in the ability to administer the subsequent cycle [14]. They also found that the OP protocol was preferred by patients and used less healthcare resources. However, a survey conducted in 2011 in many Japan oncology centres showed that very few (n=13; 4%) were administering cisplatin in an outpatient setting [15] emphasizing that cisplatin outpatient delivery is still uncommon.

Many authors have studied the optimal way to estimate easily and accurately the glomerular filtration rate in oncology [16,17]. In the field of thoracic oncology, consistent results found that the Cockcroft and Gault (CG) formula could be appropriate in most of the case for estimating the renal function, particularly if clearance range between 50-120 ml/min and before 70 years old [18,19].

Our study has some limitations. The first one is the low number of included patients, especially in the OP group. We retrospectively

calculated the power of our study and found that we have a 60% power only to detect a 10 ml/min difference in clearance level 3 weeks after the last cisplatin regimen (5% alpha risk, unilateral test). In addition, creatinine clearance 3- and 12-weeks after the last cisplatin course could be biased outcomes. Indeed, since our design is retrospective, we had many missing values for these two variables. It is thus possible that patients with available data at 3 and 12 weeks could be those with unexpected early outcomes (either related to cancer disease or to chemotherapy drugs) resulting in a supplementary (non-usual) blood sampling. Another limitation is that we did not record the actual delivered dose of cisplatin but only the planned one. Thus the true delivered dose could be different between the two groups resulting in a possible exposition bias. However, our sensitivity analysis strengthens our findings since the model computed (resulting in a matched case-control design) showed that both groups were comparable at first course of cisplatin, and produced very consistent results compared with our observed finding. We also found a significant imbalance between the two groups regarding the type of doublet drug used. However, since we adjusted our main results for the kind of doublet drug used, this imbalance should not significantly affect our main findings. However, OP group may suffer from selection bias. Indeed, physicians in the OP-centre selected drastically patients able to undergo cisplatin in outpatient clinic while others were treated with carboplatin. This leads to a less frequent choice of cisplatin-based regimen, and therefore to an imbalance in number of included patients between the two groups. In addition the IP centre has a biggest activity than the OP centre. Finally, physicians using the OP protocol paid great attention to stop (or suspend) all potentially nephrotoxic concomitant drugs as demonstrated in Table 1.

However, our study also has some strength. To our knowledge, this study is the first one to comprehensively assess renal function change in two different schedule of cisplatin administration. In addition, our study was designed in a very practical and routine-based approach.

Conclusion

Although suffering from limitations, our work provides evidence that high dose cisplatin could be safely administered for renal function at outpatient clinics. However, patients should be tightly selected and physicians should be certain of their good understanding of medical advices. Prospective randomized trials could provide better evidence and should be considered regarding the very wide use of cisplatin chemotherapy and the growing pressure on in-patients clinics.

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Authors' Contributions

SC, MC conceived of the study, and participated in its design and coordination and helped to draft the manuscript.

TS, ACT provided statistical analysis and methodological help.

GF, MC, DF, MD, ACT collected and analyzed the data.

EV participated in analyze data and gave special expertise in nephrology.

DMS, PJS coordinate the study and helped to draft the manuscript.

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