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Routine administration of a single dose of cisplatin ≥ 75 mg/m² after short hydration in an outpatient lung-cancer clinic

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Abstract. Background. Cisplatin is a pivotal drug in combined chemotherapy for non-small cell and small-cell lung cancers (NSCLC or SCLC), but its renal toxicity limits its use. Current guidelines recommend 24 h hydration: thus hospitalization is required. The aim of this retrospective study was to confirm the safety of short hydration before giving an intermediate-to-high dose of cisplatin in an outpatient clinic. **Patients and methods**. Patients eligible had NSCLC or SCLC and were being treated with a chemotherapy regimen that included cisplatin ≥ 75 mg/m². They were given the same short hydration protocol for 1 day. Nephrotoxicity was defined as ≥ grade 1 according to NCIC common toxicity criteria. Predictive factors for nephrotoxicity were analyzed. **Results**. Three hundred and fifty-seven consecutive patients (median age 58 years, range: 25-81) were reviewed. Twenty-one patients (6%) had ≥ grade 1 nephrotoxicity and all except one had **grade 1 toxicity** according to NCIC criteria for common toxicity (SC < 1,5 N). Predictive factors independently associated with nephrotoxicity included associated co-morbid conditions (hypertension, diabetes, heart disease) (OR = 4.97 CI 95% [1.8-13.7] $P = 0.002$), initial serum creatinine ≥ 100 µmol/L (OR = 8.3 CI 95% [2.55-27.4] $P = 0.0005$), and dose cycle of cisplatin ≥ 100 mg/m² (OR = 10.8 CI 95% [3.6-32.5] $P < 0.0001$). **Conclusion**. Rapid outpatient administration of a single dose of cisplatin at ≥ 75 mg/m² is feasible without a high risk of nephrotoxicity. ▲

Key words: lung cancer, cisplatin, outpatient regimen, short hydration

Introduction

A cisplatin-based combination therapy is currently considered the most active treatment option for several types of solid tumors, including lung cancer. In phase III trials, the association of cisplatin with one of the third-generation agents (paclitaxel, docetaxel, gemcitabine, vinorelbine, or pemetrexed [restricted to non-squamous histologies for the latter]) has demonstrated efficacy in patients with locally advanced and metastatic non-small-cell lung cancer (NSCLC) [1-4]. Moreover, cisplatin-based chemotherapy also significantly increased overall survival rates of patients with completely resected NSCLC [5-7]. Thus, a large proportion of patients with NSCLC are being treated with cisplatin-based chemotherapy. When cisplatin was first approved for commercial use in 1978, major causes of toxicity included severe nausea and vomiting and a high incidence of renal dysfunction. These adverse effects were reduced by the use of 5HT3-receptor antagonists and hydration [8].

Most instructions concerning hydration recommend the use of a pre-treatment regimen with 1 to 2 L of fluid infused for 8 to 12 h, with the drug diluted in 2 L of 5% dextrose, in half or one third normal saline containing 37.5 g of mannitol, and infused over a 6- to 8-h period (US Food, BC Cancer Agency). It is also recommended that hydration and control of diuresis are maintained during the following 24 h, eventually with a diuretic. Nevertheless, no consistent data exist concerning the specific protective effect of either mannitol or furosemide, or the duration of hydration [8, 9]. Ambulatory oncological care has been widely

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developed to reduce time spent in the hospital unit, one of the most important concerns for cancer patients [10, 11]. In addition, the safety of cisplatin administration to outpatients has been queried. Moreover, conventional cisplatin administration usually requires complete hospitalization in most countries. Therefore, we carried out retrospective evaluation of the safety and tolerance of treating outpatients with cisplatin between 2001 and 2007. Nephrotoxicity was considered in this report as the primary criterion for safety analysis, and the toxicity scale of NCI was based on creatinine level, as this is used in all therapeutic trials and reflects our daily oncological routine.

Patients and methods

Selection of patients

Patients eligible for the retrospective study (between January 2001 and May 2007) had NSCLC or small-cell lung cancer (SCLC) and were treated at the outpatient clinic of Tenon University Hospital with a chemotherapy regimen that included cisplatin ≥ 75 mg/m^2 with a pre-planned short hydration protocol delivered intravenously in 2 h. Patients who were consecutively treated with fractionated cisplatin ≥ 75 mg/m^2 were excluded. Study parameters included age, gender, and weight before and after each course of treatment, performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale, typing of tumor histology, stage of disease, co-morbidity (high blood pressure, cardiac insufficiency and coronary disease, diabetes, and hypercholesterolemia) and associated treatments (diuretics, angiotensin-converting enzymes [ACE] or both).

Nephrotoxicity was defined as $\geq$ grade 1 according to National Cancer Institute (NCI) common toxicity criteria. Creatininemia was measured every week and the nadir was used for evaluation of the nephrotoxicity. Rate of creatinine clearance (ΔCC) was defined as the difference between the initial calculated CC and the minimal CC recorded up to completion of the last course with cisplatin. CC was calculated using the Cockcroft and Gault formula.

Cisplatin administration

Starting at 8 a.m., patients were prehydrated with 2 L of G5%, with 4 g/L NaCl, 2 g/L KCl, 1 g/L $MgCl_2$, and 1 g/L $CaCl_2$, without control of diuresis. Cisplatin was infused in 250 mL of saline solution at 1 mg/min. Neither mannitol nor diuretics were administered. Patients were able to return home at 3 p.m. The duration at the outpatient clinic was at least 6 h. Patients were advised to drink large quantities of liquids during the days following chemotherapy.

Statistical analyses

All quantitative variables of the study were converted into categorical variables using the median as the cut-off point. Proportions were compared by the Chi^2 test or Fisher's exact test, as appropriate. A backward logistic regression was performed to assess the relationship between the patients' demography, disease characteristics, cisplatin dose, and nephrotoxicity. The fit of the logistic regression was assessed by the Hosmer and Lemeshow goodness-of-fit test. A good fit to the data was indicated by non-significance of the test. A *P*-level < 0.05 was considered significant. All analyses were carried out using SAS software version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Patients

The data from 357 consecutive patients with NSCLC or SCLC were analyzed. The patients' characteristics are shown in *table 1*. Among the 357 patients, 250 were men. The median age was 58 years (range: 25-81 years) and 7% were aged > 70 years. The ECOG PS was 0 in 80% of cases, 1 in 19% of cases, and 2 in 1% of cases. The subtype histology was NSCLC in 340 patients (adenocarcinoma: 47%, squamous cell: 27%, large cell: 10%, and others: 16%), and SCLC in 17 patients. For NSCLC, disease stage was I-II in 20% and III-IV in 80% of cases. For SCLC, the disease was localized in 45% and was disseminated in 55%. Co-morbidities

Table 1. Patients' characteristics.

	n	%
Age (years)		
Median (range)	58 (25-81)	
≥ 70 years	26	7
Gender		
Male	250	70
Female	107	30
ECOG PS		
0	286	80
1	69	19
2	2	1
Histology		
NSCLC	340	95.5
SCLC	17	4.5
Stage NSCLC	340	100
I-II	68	20
III-IV	272	80
Stage SCLC	17	100
Localized	8	45
Disseminated	9	55
Co-morbidity	95	26.5
Diuretics or ACE	41	11.5

SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; ACE: angiotensin-converting enzymes; PS: performance status.