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Individual dosing of carboplatin based on drug monitoring in children receiving high-dose chemotherapy

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Abstract

Individual dosing of carboplatin based on drug monitoring was performed within a multi-centric phase I study based on high AUC-levels in children. Twelve patients (aged 3–17 years old) have been included: 3, 5, and 4 patients at the overall target ultra-filterable carboplatin AUC of 20, 25, or 30 mg/ml×min, respectively. Carboplatin was administered as a daily 60-min infusion, repeated on five consecutive days. The initial daily dose corresponding to the three first days was calculated according to the carboplatin clearance (CL) predicted from patients' characteristics (body weight, serum creatinine and nephrectomy status). Three blood samples were taken per patient. The individual CL were estimated by MAP (maximum *a posteriori* approach) Bayesian method implemented in the MP-K program. The doses for day 4 and 5 was adjusted in order to obtain the overall target AUC. Drug monitoring led to a change in the carboplatin dose (overall administered dose versus overall dose planned) ranging from −41% to +45%. Pharmacokinetics were performed at day 5 for 7/12 children: mean relative change between day 1 and day 5 was −11% showing a statistically significant, but limited, decrease of CL from day 1 to day 5. The percentage of difference between the observed and target overall AUC ranged between −7% and +14%. Three patients (one at each AUC level) who were previously treated with cisplatin experienced dose-limiting hearing loss. In conclusion, drug monitoring and dose adjustment is needed for the control of carboplatin plasma exposure when administering high doses of carboplatin in children.

Keywords: Carboplatin; Pharmacokinetics; Bayesian analysis; Autologous bone marrow transplantation; Paediatric oncology

1. Introduction

Carboplatin is often used for the treatment of solid paediatric malignancies [1]. High-dose (HD) chemotherapy using carboplatin in combination with melphalan and etoposide followed by autologous stem-cell rescue achieved long-term survival in paediatric high-risk recurrent tumours [2]. Since relationships between systemic exposure to carboplatin and both toxicity and response have been described (reviewed in Ref. [3]), individual doses are usually adjusted according to both the target area under the concentration-time curve (AUC) and predicted carboplatin clearance for conventional treatments. The concept of AUC-dosing should be also applied for HD chemotherapy in order to avoid both under-dosing of patients with a high clearance, and unacceptable treatment-toxicity in those with a poor clearance [4], as has already been shown by Thomas and colleagues for carboplatin in children at "conventional" AUCs [5]. This can be performed using a "formula" based on patients' characteristics [6,7] or drug monitoring. Indeed, HD carboplatin is given as daily short-term infusions, repeated up to five times. Then, a therapeutic drug monitoring can be performed after the first injection in order to adjust the remaining doses according to the desired overall target AUC. Such as individual dose adjustment has already been developed for HD carboplatin in the treatment of refractory testicular cancers in adults [8]. The objective of this pharmacokinetic study was to evaluate the feasibility and the performances of

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an individual dosing methodology within a multi-centric phase I study of HD carboplatin given as a single agent in children with refractory solid tumours. The results of this study allow different methods of drug dosing in oncology to be compared in terms of the control of the plasma exposure: based on body surface area (BSA), on patients' covariates to which carboplatin clearance has been previously correlated, and on drug monitoring.

2. Patients and methods

2.1. Patients and design of the phase I clinical trial

On October 2002, twelve patients with refractory or relapsing tumours after conventional therapy have been included in this phase I study that was approved by the ethical committee I of Toulouse. Informed and written consent was obtained from the parents of all patients. The patients' characteristics are summarised in Table 1. They were treated at the Institut Curie (Paris), Institut Gustave-Roussy (Villejuif), Hôpital d'Enfants (Nancy), Hôpital d'Enfants de la Timone (Marseille) and Institut Claudius-Regaud (Toulouse). Before the administration of HD carboplatin, peripheral blood stem cells (PBSC) were harvested, either in steady-state after 3 to 6 days of granulocyte colony stimulating factor (G-CSF: 10 μg/kg/day) or after priming with chemotherapy followed by G-CSF (5 μg/kg/day during 2 to 6 days) as soon as haematological recovery began. Limiting toxicity was defined according to the National Cancer Institute (NCI) score. The maximum tolerated area under the curve (MT-AUC) included either any grade 4 haematological toxicity lasting more than 4 weeks after transplantation or any grade 3-4 extra-haematological toxicity (except mucositis and alopecia). Regarding neurological toxicity, such scores were not taken into account for patients presenting with central nervous system (CNS) tumours. Lastly, any life-threatening infection was considered as unacceptable toxicity. Escalation of AUC was considered after three evaluable patients had been included in each AUC-level.

Table 1
Characteristics of the 12 children

Patient #	Gender	Age (years)	Body weight (kg)	BSA* (m^2)	Serum creatinine (μM)	Diagnosis
1	M	14.5	52	1.6	48	Ewing's sarcoma
2	M	13.0	37	1.2	88	Osteosarcoma
3	F	17.3	54	1.5	62	Chondrosarcoma
4	F	3.2	12	0.56	42	Central nervous system tumour
5	F	2.9	13	0.58	31	Neuroblastoma
6	M	3.3	14	0.62	30	Neuroblastoma
7	M	3.1	13	0.54	27	Neuroblastoma
8	M	4.1	20	0.79	36	Neuroblastoma
9	F	3.2	10	0.49	45	Neuroblastoma
10	F	2.8	13	0.58	23	Neuroblastoma
11**	M	3.7	13	0.59	34	Neuroblastoma
12	M	3.5	15	0.65	40	Neuroblastoma
Median		3.4	14	0.61	38	
Minimum		2.8	10	0.49	23	
Maximum		17.3	54	1.6	88	

#, number; M, male; F, female. *Body surface area; **Patient with unilateral nephrectomy.

2.2. Carboplatin administration, blood sampling and platinum analysis

Carboplatin was administered as a daily 60-min infusion in 5% dextrose, repeated for five days. The initial daily dose ($Dose_{initial}$) corresponding to the three first days was calculated in order to achieve the daily ultrafiltrable carboplatin AUC (i.e., 4, 5 or 6 mg/ml×min for 3, 5 and 4 patients, respectively) in accordance with the carboplatin clearance predicted according to the following equation [9]:

$$CL\ (ml/min) = [2.92 \times body\ weight \times (1 - 0.23 \times Np) \times (1 - 0.0037 \times Scr)] + 9.6$$

with body weight (BW) in kilograms, serum creatinine (Scr) in μM, and Np = 1 or 0 for unilateral nephrectomy or not, respectively.

Three blood samples were taken per patient corresponding to three sampling windows: [0–0.5], [1–2], and [4–5] h after the end of infusion. These three samples have been selected according to a limited sampling strategy (LSS) previously developed in Ref. [10].

After immediate centrifugation at 1500 g for 10 min at 4 °C, the plasma was separated and ultrafiltered using the Amicon MPS1 micropartition system with YMT membranes at 4 °C for 20 min at 2000 g. Plasma ultrafilterable carboplatin levels were measured by means of flameless atomic absorption spectrophotometric (FAAS) analysis according to the previously described method in Ref. [11]. A cross validation was performed within the four centres of the FAAS analysis (Villejuif, Paris, Marseille and Toulouse) using seeded plasma ultrafiltrate control samples with nominal values of 1.0 and 12.0 mg/l: the inter-centre coefficients of variation for precision were 5.1 and 9.7%, respectively.

2.3. Pharmacokinetic analysis and dose adjustment within cycle

The individual carboplatin clearances (CL) was estimated from the carboplatin plasma ultrafilterable concentrations by MAP (i.e., maximum *a posteriori* approach) Bayesian method [10] implemented in the MP-K program [12], developed by one of us (s.urien@stcoud-huguenin.org). An open two-compartment model was used, and mean values and standard deviations for the population kinetic parameters were previously obtained from a group of 16 children aged from 9 months to 17.5 years (9 males/7 females) for

whom a rich blood sampling was performed after a 1-h infusion of carboplatin for the treatment of various solid tumours. The dose of the two last days (i.e., days 4 and 5), $Dose_{final}$, was adjusted in the function of the individual clearance in order to obtain the overall target AUC (20, 25 or 30 mg/ml×min): $Dose_{final} = [(\text{overall target AUC}) \times CL_{day\ 1} - 3 \times Dose_{initial}]/2$. Two blood samples at time [0–0.5], and [4–5] h after the end of infusion were obtained after administration at day 5 for 7/12 children. For these 7 patients, the observed AUC has been calculated according to the final equation (corresponding to the hypothesis that carboplatin clearance changes between day 3 and day 4): overall $AUC = 3 \times Dose_{initial}/CL_{day\ 1} + 2 \times Dose_{final}/CL_{day\ 5}$.

2.4. Extended pharmacokinetic analysis

The carboplatin concentrations *versus* time data obtained at day 5 (when available) were analysed using the bayesian method implemented in MP-K independently of those obtained at day 1. Pharmacokinetic data at day 1 and day 5 were also analysed independently using the non-linear mixed-effect model (NONMEM) [13] in order to obtain individual values for carboplatin CL by Bayesian estimation. This methodology using a database composed of data from 117 children has been previously validated for sparse carboplatin data [9].

3. Results

3.1. Comparison of carboplatin clearances obtained by Micropharm and NONMEM analysis

The value for carboplatin clearance obtained by the LSS and the bayesian analysis was not dependent on the methodology used. Fig. 1 shows the good agreement between the MicroPharm and NONMEM results. The relative prediction errors, $(CL_{NONMEM} - CL_{MicroPharm}) \times 100/CL_{MicroPharm}$, ranged between −19% and +18% and were comprised between −12% and +12% for 17/19 values. The mean difference ± standard deviation (SD) for $CL_{NONMEM} - CL_{MicroPharm}$ was 1.4 ± 6.9 ml/min which was not significantly different from zero. Only Micropharm values will be considered during the following part of the manuscript.

3.2. Intra-patient pharmacokinetic variability within cycles

Individual values of clearance are stated in Table 2. Changes in carboplatin clearance between day 1 and day 5 are shown in Fig. 1. Mean relative change was −11% (range: −37%–+5%) showing a limited, but significant ($P < 0.05$), decrease of carboplatin CL from day 1 to day 5. The value −37% was observed in patient #4 for whom amikacin treatment was given concomitantly

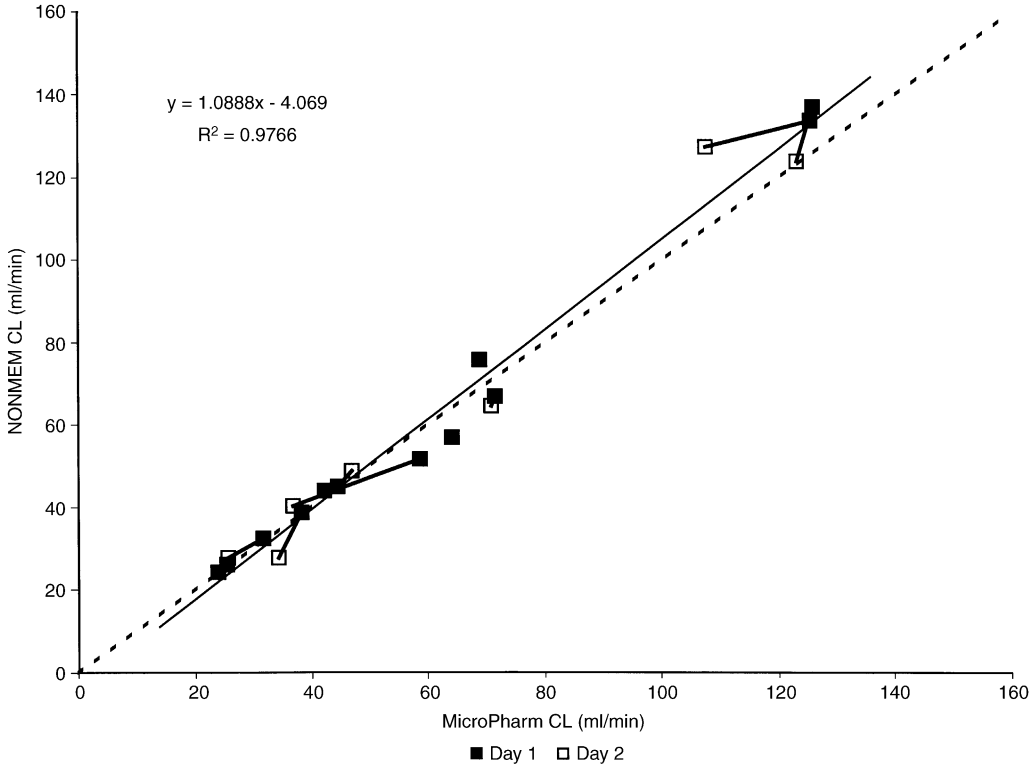

Fig. 1. Comparison of the carboplatin clearances obtained by limited sampling strategy (LSS) and Bayesian analysis using either MicroPharm or non-linear mixed effect model (NONMEM) methodology ($n = 12$ patients). Connected points illustrate the intra-patient pharmacokinetic variability within the 5-day treatment ($n = 7$ patients). The line of identity (– – –) and the linear regression line (—) are shown. CL, clearance.

Table 2
Carboplatin dosing and pharmacokinetic parameters

Patient #	Target total AUC (mg/ml×min)	Predicted CL* (ml/min)	Observed CL at day 1 (ml/min)	Observed CL at day 1 (ml/min/m^2)	Observed CL at day 5 (ml/min)	Total administered dose (mg)	Observed total AUC (mg/ml×min)
1	20	134	126	79	107	2525	21.3
2	20	82	69	57	NE**	1404	NE
3	20	132	126	82	123	2550	20.2
4***	25	40	59	105	37	1082	23.3
5	25	44	42	73	NE	1040	NE
6	25	45	64	103	NE	1600	NE
7	25	43	38	71	34	949	25.8
8	25	60	71	90	71	1800	25.3
9	30	34	32	64	26	948	34.2
10	30	44	24	41	NE	715	NE
11	30	35	25	43	NE	760	NE
12	30	47	44	68	47	1293	29.4
Mean		61.7	60.0	72.2	63.9		
Minimum		34	24	41	26		
Maximum		134	126	105	123		

AUC, area under the concentration-time curve; Np, unilateral nephrectomy; Scr, serum creatinine. *Clearance calculated according to the equation: CL (ml/min) = [2.92×body weight×(1−0.23×Np)×(1−0.0037×Scr)] + 9.6 ; **not evaluated ; ***receiving amikacin.

due to infectious disease. For this patient, drug monitoring has been performed each day because daily changes in carboplatin CL were expected; dose adjustment was calculated by taking into account the different CL values (58.7, 40.4, 40.9, 38.1 and 36.6 ml/min at days 1, 2, 3, 4 and 5, respectively). After exclusion of the data from this patient, the mean relative change of CL between day 1 and day 5 was only −7%, but was still significantly different from zero ($P < 0.05$).

3.3. Observed AUC and carboplatin dosing

Administered carboplatin doses and observed AUC are stated in Table 2. For one patient, no further carboplatin was given on day 4 and day 5, as the target AUC was already reached after 3 days. Results of drug monitoring led to a change of carboplatin dose (overall administered dose *versus* overall dose planned according to the covariates) ranged between −41% and +45%; mean value (±SD): −2% (±25%). Percentage of difference between observed and target overall AUC ranged between −7% and +14% (available in 7/12 patients). Considering only these 7 patients, changes of the carboplatin dose ranged between −16% and +19%. Fig. 2 allows one to compare the administered doses and optimal doses in order to achieve a target AUC (where the optimal dose was calculated from the mean of the observed CL at day 1 and day 5). Percentages of difference between carboplatin dose corresponding to either BSA ($Dose_{BSA}$) or covariates used for determining the initial dose ($Dose_{Covariates}$) to achieve the overall target AUC, and total administered dose have been calculated, *pe*(%), for each of the 12 children. The root mean squared relative prediction error ($rmse\% = [n^{-1}.\sum_{j=1}^{n}(pe_j^2)]^{1/2}$, where n is the number of children) as an assessment of precision of each dosing (BSA-dosing or covariates-dosing) method, was 36% and 30%, respectively. The overall AUC corresponding to $Dose_{BSA}$ or $Dose_{Covariates}$ were calculated by considering the value of observed CL at day 1 (five patients) or the mean value of observed CL at day 1 and day 5 (seven patients): percentage of difference between these AUC and target AUC ranged between −28% and +81% for $Dose_{BSA}$, and between −29% and +82% for $Dose_{Covariates}$.

3.4. Toxicity

Toxicity was mainly haematological, as expected after high-dose chemotherapy followed by autologous PBSC re-infusion, and always manageable. Briefly, grade 4 neutropenia and thrombocytopenia were observed in all patients and lasted 7 days on average with a range of 2–13 and 1–32 days, respectively. A median of two (range: 1–6) platelets and two (range: 1–3) red blood cells transfusions were necessary. Fever of unknown origin was observed in seven patients and the median duration of empirical antibiotic therapy was 8 days. No life-threatening infection was observed. No difference was observed between the three AUC levels. Extra-haematological toxicity was analysed according to each target AUC level. At level 1 (overall target AUC of 20 mg/ml×min), grade 3 vomiting was observed in one patient and grade 3 hearing loss in another. This patient had an osteosarcoma and had previously received a total dose of 500 mg/m^2 of cisplatin. Considering level 2 (AUC = 25 mg/ml×min), one patient had a grade 2 hearing loss, although he had normal audition at the

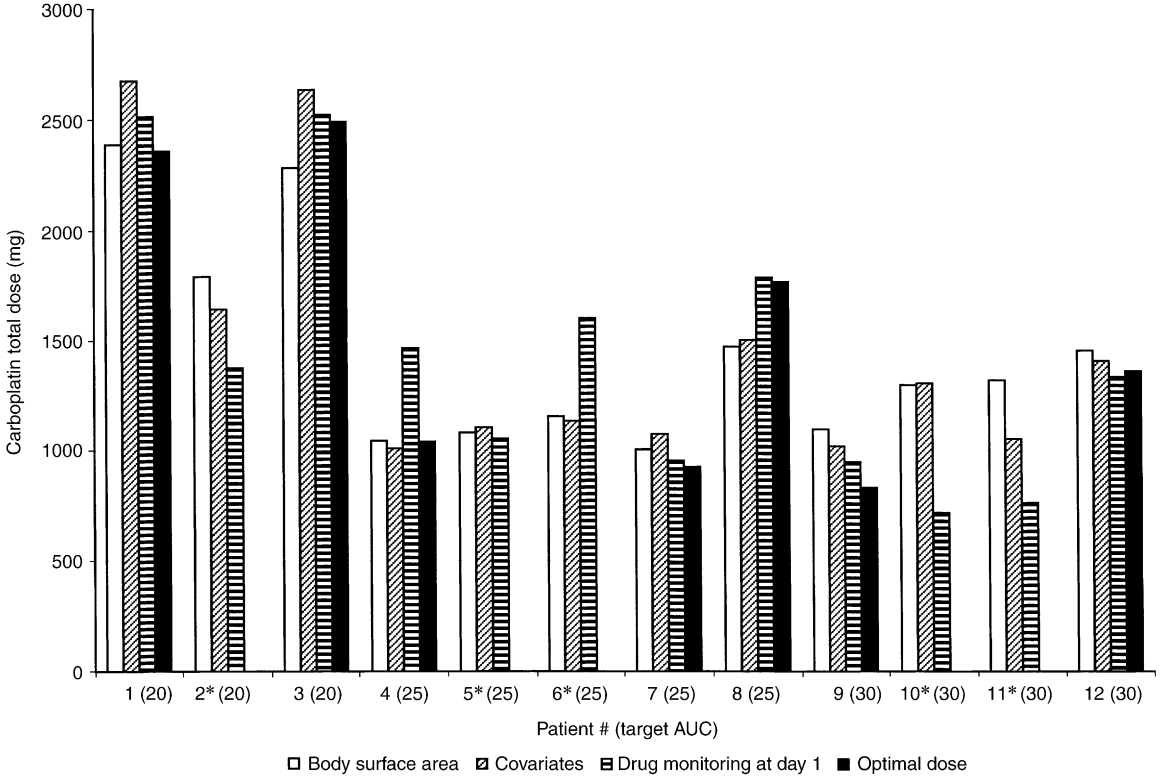

Fig. 2. Comparison of the carboplatin total dose (mg) to achieve target overall area under the concentration curve (AUC): (i) calculated according to the body surface area (BSA) (and mean value of 74.6 ml/min/m^2 for carboplatin clearance [6]); (ii) calculated according to the covariates serum creatinine, body weight and nephrectomy status (=5×administered $Dose_{initial}$); (iii) calculated from observed clearance at day 1 (=administered total dose except for patient #4); (iii) optimal dose calculated from the mean of the observed clearance at day 1 and day 5. *Patients with no pharmacokinetic evaluation at day 5.

time of inclusion. Another patient had a grade 1 auditory toxicity at inclusion which worsened to a grade 3 auditory loss after the chemotherapy course. Those two patients had been treated for a metastatic neuroblastoma and had previously received 400 mg/m^2 of cisplatin. In the level 3 group (AUC = 30 mg/ml×min), a grade 2 hearing loss was observed in one patient who had the same alteration before the administration of carboplatin. These observations led us to amend the protocol during the study: patients who had previously received a total dose of cisplatin of 400 mg/ m^2 were considered to be ineligible for the study; a loss of 2 grades in audition, whatever the initial grade, was considered as a limiting toxicity; and, further inclusions at AUC-level 2 were performed. Renal function was not impaired except for the grade 2 or 3 tubular toxicities with transient potassium or magnesium urinary losses that were observed in three children, but these resolved rapidly.

4. Discussion

During this phase I study, carboplatin doses were individually adjusted and AUC escalation was performed rather than dose (in mg/m^2) escalation. Indeed, the mean doses (in mg/m^2) were 1472, 2068 and 1611 at AUC levels of 20, 25 and 30 mg/ml×min, respectively. The lower dose at AUC level 30 was as a result of a lower mean carboplatin CL of children included at this AUC level. Thus, the term ''high AUC chemotherapy'' would be more appropriate than ''high dose chemotherapy''. Since plasma drug monitoring at day 1 represented a determinant (and final) criteria for individual dose adjustment within cycles, we have compared the Bayesian method (using the MP-K) [12] with another published Bayesian method (using the NONMEM program) applied to carboplatin pharmacokinetic data in children [9]. MicroPharm and NONMEM values did not differ, both statistically and clinically (Fig. 1), confirming the reliability of the individual carboplatin CL data obtained. Use of the MP-K program was preferred during this multi-centric study for the additional analyses, as this program was more user-friendly.

The intra-patient variability in carboplatin CL between day 1 and day 5 was evaluated in 7/12 patients and was statistically significant, but limited: percent change of CL ranged between −19% and +5% (mean: −7%) if the data for #4 was excluded. Consequently,

the administered doses (calculated according to the result of the day 1 drug monitoring) were consistent with the optimal doses to obtain target AUC. However, dosing according to the body surface area BSA would have been associated with large differences between the expected and actual AUCs. By taking into account the covariates (i.e., serum creatinine level, body weight and nephrectomy status), the precision of carboplatin dosing was only slightly improved in comparison with the BSA-based dosing (precision of 30% for covariates-based dosing *versus* 36% for BSA-based dosing). Indeed, the benefit of using covariates is particularly important for patients with a poor renal function [5]. However, no child in the present study had this characteristic. Overall, drug monitoring allowed us to control the total carboplatin AUC much better than methods based on BSA or covariates would have done: percentage of difference in AUC ranged from −7% to +14% (available for 7/12 patients) for drug monitoring *versus* from −29% to +82% for the dosing method based on covariates. Mean observed AUCs were 20.7, 24.8 and 31.8 for target values of 20, 25 and 30 mg/ml×min, respectively. The pharmacokinetic evaluation performed at day 5 in 7 patients showed that drug monitoring at day 1 would be sufficient. However, patients receiving other nephrotoxic drugs, such as amikacin, may require daily monitoring.

Thomas and colleagues [5] performed an individual dosing of HD carboplatin in children based on renal function using a determination of the glomerular filtration rate by an isotopic tracer clearance method, ie, ^{51}Cr-ethylene diamine tetra acetic acid (EDTA). This dosing method was superior than that based on BSA: 74% of courses had an observed AUC within ±20% of the target value, versus 49% for BSA. However, the isotopic determination requires as many blood samples as we did for the determination of the carboplatin CL during our study. The pharmacokinetic data obtained at day 5 for 7/12 indicated that carboplatin drug monitoring would be more efficient at controlling the overall AUC than ^{51}Cr-EDTA.

The toxicity results observed during this study do not allow us to define the maximum tolerated AUC, and further inclusions are planned. However, we have already observed that hearing loss is a dose-limiting toxicity. It is likely to occur in children who have been pre-treated with cisplatin. This "pharmacodynamic" characteristic (i.e., cisplatin pre-treatment) appears more important than the AUC, since auditory loss has been observed at each AUC level. We may also conclude that the use of an overall target AUC of 20 mg/ml×min of carboplatin, as is often used in children, remains empirical, and larger values may be targeted. The pharmacokinetic results show that drug monitoring is necessary to control individual plasma carboplatin exposure. Use of such methodology should be encouraged for HD chemotherapy consisting of repeated daily administrations. We have shown this approach may be feasible, even at a multicentre level, (with, for some patients, an analytical site different from the treatment place). Moreover, the limited number of patients undergoing HD chemotherapy would allow systematic, individual monitoring to be performed.

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