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Early detection of acute cisplatin nephrotoxicity: interest of urinary monitoring of proximal tubular biomarkers

Valérien Bunel¹, Yasmina Tournay², Thomas Baudoux^{1,2}, Eric De Prez¹, Marie Marchand³, Zita Mekinda⁴, Raphaël Maréchal⁵, Thierry Roumeguère⁶, Marie-Hélène Antoine¹ and Joëlle L. Nortier^{1,2}

¹Laboratory of Experimental Nephrology, Faculty of Medicine, Université Libre de Bruxelles, Brussels, Belgium,

²Department of Nephrology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium, ³Department of Oncology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium, ⁴Department of Pneumology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium, ⁵Department of Gastroenterology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium and ⁶Department of Urology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

Correspondence and offprint requests to: Joëlle L. Nortier; E-mail: Joelle.Nortier@erasme.ulb.ac.be

Abstract

Background: Renal toxicity induced by cisplatin (CisPt) is a clinical issue in patients with or without chronic kidney disease (CKD). Proximal tubular injury can result in acute kidney injury (AKI), which may compromise the course of chemotherapy and the prognosis. The purpose of this study was to investigate the time course of urinary markers of acute tubulotoxicity and to assess the usefulness of such monitoring in a routine clinical setting.

Methods: This work is an open prospective pilot study carried out among 23 patients receiving a platinum-based chemotherapy. Individual comorbidities, plasma parameters of kidney function (urea, creatinine) and estimated glomerular filtration rate were registered. Urinary excretion of leucine aminopeptidase, neutrophil gelatinase-associated lipocalin, cystatin C, liver fatty acid-binding protein and interleukin-18 were monitored during successive chemotherapy cycles. Episodes of AKI were identified according to KDIGO (Kidney Disease Improving Global Outcomes) 2012 guidelines.

Results: A total of 28 patients were recruited; among them 23 agreed to be part of the study, of whom 18 received CisPt and 5 carbo- or oxaliplatin. Of the 18 CisPt patients, 12 had a preexisting CKD. Sixteen AKI episodes were observed in 13 patients receiving CisPt with a pejorative evolution in seven cases (partial recovery of the renal function); a transient but dramatic increase in urinary biomarkers was observed 3 h after chemotherapy initiation, whereas plasma creatinine rise appeared 72 h after the end of CisPt treatment. Identified precipitating factors included: dehydration due to lack of fluid intake or diuretic use, exposure to high CisPt doses, regular use of nonsteroidal anti-inflammatory drugs and/or iodinated contrast agents and sepsis.

Conclusion: Even if numerous precipitating factors could be avoided, the monitoring of urinary markers seemed helpful for the early detection of subclinical AKI induced during CisPt chemotherapy.

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Key words: AKI, biomarkers, cisplatin, creatinine, nephrotoxicity

Introduction

Cisplatin (CisPt) is an alkylating drug that has been successfully used for decades to treat solid organ tumours such as lung, testis or ovarian cancers, resulting in an increased life expectancy for patients. The effectiveness of CisPt can partly be explained by formation of adducts with nuclear and mitochondrial DNA, which inhibits tumour cell growth and proliferation, and triggers their death. Other key mechanisms concurring to the cytotoxic activity of CisPt include the formation of adducts to RNA, phospholipids and thiols-bearing proteins, reaction with and depletion of intracellular glutathione, and enhancement in the oxidative status [1].

However, these processes happen not only in tumour cells but also in renal proximal tubular epithelial cells (RPTECs), where CisPt accumulates and exerts its toxicity [2, 3]. Indeed, during chemotherapy cycles, high numbers of RPTECs die, resulting in a transient and not fully reversible loss of kidney structure and function called acute kidney injury (AKI) [4, 5]. Other phenomena involved in the renal toxicity of CisPt include disturbance in the intrarenal haemodynamics, which contributes to the decrease in the glomerular filtration rate (GFR) [6]. Finally, the increased expression of pro-inflammatory cytokines promotes differentiation, maturation and activation of white cells, and their subsequent infiltration in the interstitium [5, 7, 8].

Defects in the regeneration processes can lead to severe tubular atrophy, followed by the production of a fibrotic scarring tissue that constitutes the end point of the acute damage, and sets the basis to the progression of the chronic kidney disease (CKD) [9]. Recurrent AKI episodes, such as those experienced during chemotherapies, are generally transient but not fully reversible, and tend to become more severe and last longer with repeated injections of CisPt. In order to minimize the risk of adverse events, platinum derivatives such as carboplatin or oxaliplatin have been developed; their pharmacokinetic profiles and their antitumour spectrum are slightly different, and the risk of AKI generally appears at higher doses [10].

AKI remains a real problem for the clinician, in particular in elderly patients with preexisting CKD. Clinical data indicate that a single injection of CisPt results in a transient episode of AKI in about 20–30% of cancer patients [5, 11]. In such cases, avoiding high doses is an efficient solution for kidney preservation, but is also at risk of compromising the course of chemotherapy protocols as well as the patients' vital prognosis. Conservative approaches consist notably of: predicting an eventual underlying CKD; withdrawing drugs having deleterious effects on the intrarenal haemodynamics; or ensuring a forced diuresis of the patient by means of a sufficient hydration before, during and after CisPt administration [12].

The early detection of kidney lesions is of utmost importance to allow clinicians to adjust the posology in a dual perspective: (i) preserve the functional integrity of the kidney and (ii) reduce the risk of side effects arising from impaired pharmacokinetic parameters (notably the excretion of drugs) associated with AKI. Until recently, the monitoring of the renal function in cancer patients was limited to the evaluation of plasma creatinine (Pcr) concentration and occasionally to its clearance calculation. However, Pcr elevation is delayed for several hours to a few days after the initial renal damage and GFR drop; this routine biological parameter cannot be considered as a suitable

(early) predictive marker of kidney dysfunction. Biomarkers for which urinary excretion increases 24–48 h prior to the Pcr increase include kidney injury molecule-1 [13], neutrophil gelatinase-associated lipocalin (NGAL) [14–16], cystatin C (CyC) [17], liver fatty acid-binding protein (L-FABP) [18] and interleukin-18 (IL-18) [19]. Leucine aminopeptidase (LAP), an enzyme from the brush border of RPTECs, is also used for the detection of proximal tubular structural lesions [20].

The purpose of the present study is to investigate the time course of urinary biomarkers of acute proximal tubulotoxicity and to appreciate the usefulness of such monitoring during CisPt-based chemotherapies.

Materials and methods

Study design

This is a non-randomized open prospective monocentric pilot study supervised by the Belgian Ministry of Health in the scope of the National Cancer Plan (grant number PNC 24-015) and approved by the Ethics Committee of Erasme Hospital (Brussels, Belgium) on 22 April 2009 (ref P2009/028, ref CCB: B40620095665). The patients were recruited between May and July 2009.

Patients

In all, 23 patients aged 18–78 years suffering from a cancer requiring platinum-based treatment (CisPt, carboplatin or oxaliplatin) were enrolled. Patients presenting multiple myeloma or renal cancer were excluded. Informed consent was obtained for each patient, and their respective oncologists were informed prior to the start of the study.

Data collection

Patients charts were systematically reviewed in order to gather the following data: age, gender, cancer type, past history of urological or renal disorders (AKI episodes, CKD), cardiovascular comorbidities and ongoing medication intake when platinum was administered [in particular nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics, nephrotoxic antibiotics and iodinated radiocontrast agents].

Clinical events observed during the 2-month study period were listed, with a particular focus on AKI, episodes of which were considered positive according to the KDIGO 2012 guidelines, i.e. when (i) Pcr increased by 0.3 mg/dL or more within 48 h, (ii) Pcr was 1.5 times higher than the baseline or more within the last 7 days or (iii) urine output was <0.5 mL/kg/h for 6 h [21]. Due to technical limitations, the last KDIGO criterion was not used in this study. Other clinical events were classified according to their eventual impact on the renal function and were analysed in relation to changes in plasma and urinary biomarkers.

Biological parameters

During successive chemotherapy cycles, plasma samples were collected daily for the determinations of urea, creatinine and magnesium (as required by oncologists for assessing biological parameters) and analysed at the Central Laboratory of

Erasmus Hospital. Kidney function was monitored using plasma concentrations of urea and creatinine, and via calculation of the estimated GFR (eGFR) according to the abbreviated Modification of Diet in Renal Disease (MDRD) equation.

Urinary samples were collected before the initiation of chemotherapy for baseline evaluation and at several time points after CisPt injections. Urinary concentrations of biomarkers were determined at the Laboratory of Experimental Nephrology (Faculty of Medicine, Erasme campus, Université Libre de Bruxelles).

Urinary biomarkers

Urinary biomarkers used for the early detection of AKI included LAP, NGAL, CyC, L-FABP and IL-18. Excretion of LAP was measured with a spectrofluorimetric method as detailed previously and expressed in $\mu\text{mol AMC}$ (7-amino-4-methyl-coumarin) produced/mmol of creatinine/h [22]. Other markers were quantified using ELISA kits following the manufacturer's recommendations: NGAL assay kit was obtained from BioPorto Diagnostics (Gentofte, Denmark), Cyc assay kit came from R&D Systems (Minneapolis, MN, USA), L-FABP kit from HyCult Biotechnology BV (Uden, The Netherlands) and IL-18 kit from Medical and Biological Laboratories (Nagoya, Japan).

The results were normalized against urinary creatinine (Ucr) excretion.

Results

AKI is a common complication induced by CisPt chemotherapy

Of 28 recruited patients, 23 accepted inclusion in the study; their characteristics are detailed in Table 1. Among them, 18 have received CisPt and 5 carbo- or oxaliplatin. Of the 18 CisPt patients, 12 had a preexisting CKD according to MDRD equation (stage 2 for eight of them and stage 3 for four others).

Table 1. Clinical characteristics of the patients and related chemotherapy

Number of patients	23 (5 prevalent, 18 incident)
Mean age (years)	61 (min-max: 44–79)
Gender ratio F/M	9/14
Comorbidities	
CKD	12/23: second stage (8), third stage (4)
HTA	12/23: ACEIs (4), ARBs (2), diuretics (3)
Hypercholesterolaemia	11/23
Type 2 diabetes	1/23
Active smoking	13/23
NSAIDs	4/23
Cancer site	
Lung	14/23
Digestive tract	5/23
Gynaecological tract	2/23
Urological tract	1/23
Undetermined	1/23
Chemotherapeutic drug	
CisPt	18 patients (40–100 mg/m ²)
Carboplatin	Three patients (AUC (area under curve) 5 mg/mL/min with Calvert formula)
Oxaliplatin	Two patients (85 mg/m ²)

HTA, hypertension.

In agreement with the recommendations, all the patients were submitted to pre- and post-chemotherapy hydration protocols. Due to a high heterogeneity of methods applied arising from the type of cancer to be treated (volume and duration of perfusion of saline solution, use of mannitol or furosemide, systematic monitoring of diuresis, etc.), no correlation between the rates of adverse events and the protocol applied could be highlighted.

Furthermore, none of the five patients receiving carbo- or oxaliplatin developed any obvious sign of renal failure. Among the 18 patients receiving CisPt, 16 episodes of AKI were observed in 13 patients with a pejorative evolution in 7 cases (partial recovery of renal function). Identified precipitating factors are listed in Table 2, and are strikingly dominated by a severe dehydration due to an inadequate fluid intake and/or the use of diuretics (9/10) at the very start of chemotherapy; this observation was frequently associated with the absence of fluid administration at day 2 of the cycle (9/16 AKI episodes). Other precipitating factors include exposure to high doses of CisPt ($\geq 70 \text{ mg/m}^2$, 8/10), regular use of NSAIDs and/or iodinated contrast agents (6/10) and sepsis (3/10).

A summary of the major clinical events observed in the studied cohort is displayed in Table 3. For seven patients, major adverse effects [AKI (four) and neutropenia (three)] required the initial dose to be reduced during the following chemotherapy cycles. In another pool of nine patients, cancellation or postponement of the next chemotherapy cycle was required because of severe adverse effects, including AKI (four), neutropenia (three), infectious complication (two) or epilepsy (one). Finally, in another patient, CisPt-vinorelbine chemotherapy had to be switched to carboplatin-gemcitabine due to the severe aggravation of a preexisting polyneuropathy.

Selected urinary biomarkers can predict AKI earlier than Pcr

On one hand, all patients who developed clinically detectable AKI (highlighted by Pcr increase) also showed transient but dramatic increases in most of the monitored urinary biomarkers. Indeed, peaks were observed as soon as 3–6 h after the initiation of CisPt administration, with magnitude increases ranging from 5 to 100 times as compared with baseline for LAP, NGAL and L-FABP. In general, fluctuations in urinary concentrations of CyC and IL-18 were difficult to interpret because basal levels were sometimes greater than those observed during the cycle, and elevations were not as high as the ones displayed by LAP, NGAL or L-FABP.

On the other hand, Pcr increase became relevant and associated with AKI according to KDIGO criteria only 3–6 days after the initiation of the cycle. By that time, urinary biomarkers have usually returned to their baseline values. A relevant example is provided in Figure 1: for this patient (#3), two episodes of AKI

Table 2. Identified precipitating factors of AKI episodes (n cases)

High CisPt doses: 80 mg/m ² (6); 70 mg/m ² (2)
Preexisting CKD (four patients at third stage)
Dehydration at the start of CisPt administration (6)
Diuretics (mannitol/lasix) used during chemotherapy (8)
Regular NSAIDs intake (3)
Iodinated contrast agents (3)
Sepsis—antibiotics (2)
Regular ACEIs or ARBs or diuretic intake (2)
Bisphosphonates (1)

Table 3. Summary of the major clinical events due to adverse reactions resulting from platinum-based chemotherapy

Patient	AKI episodes	GFR ^a (mL/min/1.73 m ²)	Drug	Total dose per cycle	Cycle protocol	Protocol modifications	Identified precipitating factors
#1	1	>90 → 73	CisPt	80 mg/m ²	40 mg/m ² /day—d1, d2—1x/3 week	Epilepsy and neutropenia: third cycle postponed by 1 week	
#2	1	83 → 76	CisPt	70 mg/m ²	35 mg/m ² /day—d1, d2—1x/3 week		
#3	2	>90 → 36	CisPt	80 mg/m ²	40 mg/m ² /day—d1, d2—1x/3 week	Infection: d8 of first cycle cancelled; AKI: d8 of first and second cycles cancelled	Dehydration (insufficient fluid intake + diuretics) + NSAIDs + ceftazidime
#4	1	80 → 47	CisPt	80 mg/m ²	40 mg/m ² /day—d1, d2—1x/3 week	AKI: d8 of second cycle postponed by 6 days + 80 → 60 mg/m ² at third cycle	First stage CKD + dehydration (insufficient fluid intake + diuretics)
#5	0	75 → 68	CisPt	50 mg/m ²	1x/2 week	Neutropenia: 50 → 40 mg/m ² at third cycle; no CisPt at fourth cycle	
#6	0	>90 → >90	CisPt	70 mg/m ²	1x/3 week	Neutropenia: fourth cycle postponed by 1 week + d8 of fourth cycle postponed	
#7	0	89 → >90	CisPt	50 mg/m ²	1x/2 week		
#8	0	70 → 53	Carboplatin	AUC 5 mg/mL/min	1x/3 week	Infection: third cycle postponed by 1 month	
#9	0	9 → 64	Carboplatin	AUC 5 mg/mL/min	1x/3 week		
#10	1	>90 → 39	CisPt	80 mg/m ²	40 mg/m ² /day—d1, d2—1x/3 week	Neutropenia: d8 of first cancelled + 80 → 70 mg/m ² at second cycle	Dehydration (preexisting + diuretics + vomiting)
#11	2	>90 → 46	CisPt	80 mg/m ²	40 mg/m ² /day—d1, d2—1x/3 week	AKI: d8 of sixth cycle postponed by 1 week	Diuretics
#12	2	>90 → 76	CisPt	80 mg/m ²	40 mg/m ² /day—d1, d2—1x/3 week		Diuretics
#13	1	>90 → 41	CisPt	80 mg/m ²	40 mg/m ² /day—d1, d2—1x/3 week		Iodinated radiocontrast agents + dehydration (diuretics, vomiting) + NSAIDs
#14	0	>90 → 53	Carboplatin	AUC 5 mg/mL/min	1x/3 week		
#15	1	81 → 48	CisPt	80 mg/m ²	40 mg/m ² /day—d1, d2—1x/3 week		
#16	0	>90 → >90	CisPt	100 mg/m ²	20 mg/m ² /day—5 day/week—1x/3 week		
#17	0	77 → >90	Oxaliplatin	85 mg/m ²	1x/2 week		
#18	1	58 → 41	CisPt	70 mg/m ²	35 mg/m ² /day—d1, d2—1x/3 week	AKI: 70 → 60 mg/m ² at second cycle	Second stage CKD + iodinated radiocontrast agents + dehydration (preexisting + diuretics)
#19	0	>90 → >90	CisPt	70 mg/m ²	35 mg/m ² /day—d1, d2—1x/3 week		
#20	1	>90 → 52	CisPt	80 mg/m ²	40 mg/m ² /day—d1, d2—1x/3 week		Dehydration (preexisting + diuretics) + NSAIDs
#21	1	73 → 41	CisPt	50 mg/m ²	1x/2 week	AKI: second cycle postponed by 1 week + 70 → 60 mg/m ² at second cycle	First stage CKD + dehydration (preexisting + diuretics) + ACEIs
#22	1	58 → 61	CisPt	40 mg/m ²	1x/2 week	AKI: no CisPt during second cycle (5-fluorouracil only)	Second stage CKD + iodinated radiocontrast agents + ACEIs
#23	0	>90 → >90	Oxaliplatin	85 mg/m ²	1x/2 week		

^aGFR was estimated at the beginning and at the end of treatment by the use of MDRD equation. d = day of the week at which chemotherapy administration was initially scheduled.

developed, respectively, at days 8 and 3 of the first and second chemotherapy cycles. Higher urinary excretions of LAP and L-FABP were detected after 6 and 12h, respectively, following the administration of CisPt during the first cycle. During the second cycle, LAP and L-FABP increased 3 days and 6h, respectively, after administration of CisPt. For this patient, urinary excretion of CyC became relevant only after day 6 of the second cycle, and did not allow for a sooner prediction of AKI as compared with Pcr. A similar observation was made for the urinary excretion of NGAL, which somewhat raised after day 3 of the second cycle.

Similar conclusions were made in patient #2 (Figure 2), for whom the Pcr rise, and thus AKI, became evident on day 7 following the CisPt administration of the first cycle. However, as a reflection of tubular damage, all the biomarkers were excreted at moderate-to-higher rates (2- to 15-fold increases) as soon as 6 h following chemotherapy initiation, confirming their usefulness for the early prediction of renal failure. Indeed, if their elevations occurred rapidly, they normalized within a few days, when only Pcr levels remained high.

During the second and third cycles, rather similar (but not identical) patterns were observed, with IL-18 and CyC urinary levels rising at a lower magnitude and with a longer delay.

Urinary excretions of biomarkers could be easily identified as they represented a 6- to 60-fold increase in comparison with the baseline for LAP, 5- to 80-fold for NGAL, and 5- to 100-fold for L-FABP. However, the high variability in baseline concentrations in IL-18 and CyC hampered the interpretation and the possible correlation with AKI.

As displayed in Figures 1–3, LAP enzymuria increased generally 3–6h after exposure to CisPt, and NGAL and L-FABP also displayed rather similar time courses (rises starting as soon as 3h and peaks observed at 6–12h after exposure). In these particular cases, IL-18 and CyC kinetics do, however, display a similar pattern.

Selected biomarkers can reveal subclinical renal lesions

Even in patients for whom Pcr remained stable over 3 days following the administration of CisPt—and thus for whom clinical signs of AKI were not seen—detectable fluctuations of one or several biomarkers excretion could almost always be noticed (9/10). Indeed, their urinary concentration increased in a range from 2- to 10-fold as compared with their respective baselines.

For instance, during the second cycle of chemotherapy, patient #1 (Figure 3) featured early increases in LAP, NGAL and L-FABP excretion rates, which were somewhat lower in magnitude in comparison with AKI patients. For this patient, increased excretions of the same markers were observed during the first and third cycles, but were not sufficient to be considered as relevant. Interestingly, their rise coincided with that of IL-18 which, for this particular case, appeared as an effective predictive marker as its urinary excretion increased 24h after CisPt injection and remained high for several days. Pcr elevation was moderate across first and second cycles; it only became significant during the third cycle, thus confirming AKI diagnosis.

These observations made in patient #1 suggest that renal function did not fully recover between CisPt administrations. Indeed, acute injuries to proximal tubules were highlighted via the dramatic increase in IL-18, and, to a lesser extent via the concomitant moderate-to-high elevations in LAP, NGAL and L-FABP. If normalization of their excretion could indicate that RPTECs did not suffer any longer, regeneration of the tubules did not seem to be fully achieved: the delayed Pcr rise indicated that the overall renal function was still impaired. This also reminds us of the transient character of biomarkers excretion, which may normalize several days prior to Pcr rise.

Furthermore, two patients (#6 and #9 receiving CisPt and carboplatin, respectively) showed atypical elevations in NGAL and CyC that correlated with elevations in L-FABP (#6) and with IL-8

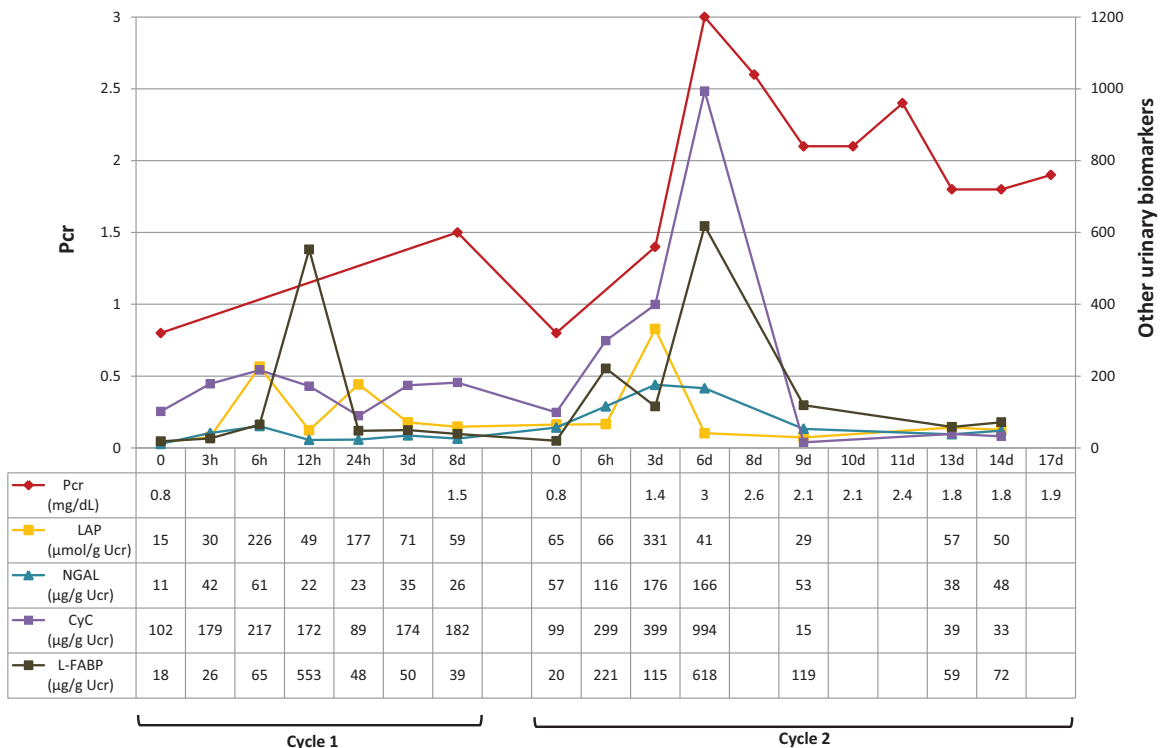


Fig. 1. Time course of Pcr and urinary biomarkers excretion in patient #3.

of NGAL, IL-18 and L-FABP were excreted. Unfortunately, no data concerning urinary LAP could be obtained, and Pcr was only assessed 8 days later; an AKI episode might thus have been missed.

Discussion

Despite the effectiveness of CisPt in improving a patient's life expectancy, acute renal toxicity remains a real problem for the clinician. One would argue that AKI is a 'necessary price to pay' for an effective chemotherapy, but in our small patient cohort, 6/13 patients had their initial CisPt dose reduced or a cycle postponed due to AKI, jeopardizing the treatment's efficacy. Therefore, oncologists should not underestimate the importance of renal function preservation, and should keep in mind that recurrent episodes of AKI (such as those occurring during chemotherapies) tend to become more severe and last longer with repeated injections of CisPt and can ultimately lead to advanced stages of CKD.

Furthermore, it is important to remember that any renal dysfunction (e.g. CKD) preexisting when CisPt chemotherapy is started may induce tubulo-interstitial lesions, which may further evolve towards interstitial inflammation and fibrosis. For this reason, the identification of biomarkers that could predict renal lesions as early as possible is of prime importance. These could help oncologists and nephrologists to agree on possible adjustments of the chemotherapy cycles in order to preserve kidney function without compromising anticancer drug efficacy (adapted doses to GFR, longer recovery periods between cycles, systematic diuresis monitoring, switch from CisPt to carbo- or oxaliplatin, etc.).

Indeed, despite the limited number of patients included in this study, several observations have been made and deserve further investigation.

Evaluation of the risks of renal damage prior to CisPt administration

In our small cohort of patients, numerous precipitating factors have been pointed out, and their avoidance could probably have resulted in a lower number of AKI episodes [72% (13/18 patients) versus 20–30% as reported in the literature]. This incidence rate is dramatically high as compared with those usually reported; it should be remembered that the onset of CisPt-induced AKI is largely dependent on the presence of predisposing factors as well as underlying or underestimated CKD. Renal manifestations are clearly more frequent when treatment is prolonged and repeated; the negative impact of recurrent episodes of dehydration also favours the onset of AKI.

In the present study, the AKI episodes observed have a multifactorial aetiology and mostly happen when high doses of CisPt are administered (80 mg/m² for 7/10 patients) and in patients who are in a dehydrated state when treatment is initiated (7/10 cases). It is important to remind clinicians that the integration of suitable hydration protocols alongside CisPt treatment is a cornerstone for adverse effects avoidance: such strategies should schedule hydration solution administration 12 h before and during the chemotherapy cycle and up to 1 day after it, preferentially using 100 mL/h of normal saline solution (0.9% NaCl rather than 0.45 NaCl + 5% glucose), and avoid the concomitant administration of diuretics whenever possible [12]. Because of their negative impact on intrarenal haemodynamics, the prescription of NSAIDs, ACEIs and/or ARBs should be prohibited whenever possible and injections of iodinated radiocontrast agents should ideally be substituted.

Moreover, in patients at risk of AKI, or those having a preexisting CKD, therapeutic alternatives such as carbo-

oxaliplatin, either alone or in combination, should be proposed if they exist. In a study comparing the rates of adverse events associated with high-dose CisPt (120 mg/m²) or with moderate-dose CisPt (60 mg/m²) plus carboplatin (200 mg/m²), high-dose CisPt was associated with more renal (36% versus 19%), auditive (16% versus 4%) and neurological (16% versus 0%) toxicity without any difference in response rates (21% versus 23%) [23]. However, CisPt remains the most potent drug as compared with platinum derivatives, notably for the treatment of non-small cell lung cancer, in terms of response and survival [24].

Furthermore, in patients suffering from CKD and elderly people who often cumulate cardiovascular comorbidities such as hypertension or diabetes, a 24-h urine collection can eventually confirm the estimation of creatinine clearance, set baseline values for biomarkers and bring other valuable information about kidney function. As a matter of fact, a retrospective study has shown that among 4684 cancer patients, 57% had a mild-to-moderate renal insufficiency (60 < GFR < 90 mL/min/1.73 m²) although 7% had an increased Pcr (>1.1 mg/dL) [25]. Among the 7181 chemotherapy prescriptions, 53% required dosage adjustments because of renal failure.

Also, sepsis should be efficiently controlled because of its potential impact on the renal function, and because the antibiotics generally used in such settings (aminoglycosides, cephalosporins) are nephrotoxic. In order to monitor the hydration state of patients on a daily basis, simple measures can be implemented: bodyweight and diuresis follow-up with an estimation of fluid intakes and excretion.

Finally, a basic renal imaging (echography) could help highlighting morphological abnormalities such as a solitary kidney (of primary origin or secondary to the surgical removal of one kidney), cortical atrophy with loss of cortico-medullary differentiation due to long-term hypertension for instance.

The need for stronger collaborations between clinicians appears essential. Indeed, for several cases included in this study, a nephrologist could have identified patients at risk of AKI, those already suffering from CKD or medications/practices known to increase the risk for CisPt-induced AKI. Furthermore, assessing the hydration state of the patient prior to the chemotherapy and ensuring proper hydration with saline in order to induce a vigorous diuresis before, during and after the cycles appears to be of prime importance. The application of these recommended conservative measures might undoubtedly have contributed to reduce the proportion of patients developing AKI.

Other possible strategies consist in dividing a daily dose over 5 days instead of administering it as a single infusion, or limiting the cumulative dose to 120 mg/m² of body surface area [26].

Finally, regeneration processes should not be overlooked; leaving sufficient time between each chemotherapy cycle may result in adequate tubular regeneration and kidney function recovery. Regenerative treatments have been successfully applied for the reduction of CisPt-induced AKI incidence in laboratory animals. These notably include mesenchymal stem cell transplantation, which can differentiate into renal tubular epithelial cells and contribute to regeneration of tubules, or erythropoietin treatment, which probably activates mesenchymal stem cells expansion and migration from bone marrow [7].

Monitoring of kidney function in the course of chemotherapy

The time course study of urinary biomarkers excretion is a non-invasive tool for the early detection of renal lesions, which can

also be used to follow up its degree of severity as well as its reversibility.

In this study, we demonstrated that during episodes of AKI induced by CisPt treatment, all urinary markers of proximal tubulotoxicity increased within hours after chemotherapy initiation.

Interestingly, urinary peaks of the biomarkers were generally transient and normalized within several days; at that time, Pcr remained elevated. This is exemplified in patient #3 (Figure 1), who excreted moderate-to-high levels of LAP, NGAL and L-FABP early after the beginning of the first chemotherapy cycle. These markers returned to baseline values after 1–3 days, suggesting that tubules had partially recovered from the acute injury. On the other hand, Pcr, which was elevated only on the eighth day of the first cycle and returned to a baseline value between the first and second cycles, seemed to indicate that the renal function had recovered. This was confirmed by means of the eGFR, which dropped from >90 to 47 mL/min/1.73 m² only 7 days after CisPt administration, and returned to >90 mL/min/1.73 m² before the second cycle start (10 days later). Upon re-administration of CisPt, Pcr remained elevated and eGFR collapsed from >90 to 36 mL/min/1.73 m², indicating that renal function did not recover after this second chemotherapy cycle. The following injections were cancelled and the patient was admitted in a palliative care unit.

Biomarkers are to be considered as biological parameters and therefore subject to variability. Patterns of excretion were found to be different among the studied population; the magnitude and the dynamics of their urinary excretion, if any, may thus largely vary from a patient to another. However, including a baseline assessment of each biomarker before the cycle starts allows individual evaluation of the initial condition, and reflects RPTECs' integrity. Any increased excretion might then be compared with these baseline conditions, and the prediction of AKI (or the identification of subclinical renal damage) appears thus possible based on the determination of two or more biomarkers.

These preliminary findings deserve to be confirmed in a larger population, and further investigations should aim at validating the predictive capacity and setting thresholds (preferably as fold increases) for the studied urinary biomarkers. Considering the pro-inflammatory profile of IL-18 and the rather difficult interpretation of CyC fluctuations, we would restrict our selection of markers to LAP, NGAL and L-FABP.

To date, the early identification of AKI through urinary biomarkers elevation remains seldom exploited and limited to clinical trials; a generalization of its use in clinical practice would surely result in treatment modifications during chemotherapy that would prevent or minimize the deleterious effects on kidneys. Cost-effectiveness is another parameter to consider in clinical practice. In this respect, in-house laboratory methods, such as LAP spectrophotometric determination, are cheaper than NGAL or L-FABP determinations, which are performed via an ELISA method, and would surely be preferred.

Furthermore, in our study, several patients exhibited an increase in urinary biomarkers without any Pcr elevation, which reveals that silent forms of AKI may probably be overlooked. For these patients, an increase in Pcr was frequently observed during the following chemotherapy cycle; a reduction of CisPt doses, justified by the biomarkers rise, could have been proposed in order to prevent AKI during the following cycle.

Conclusions

Preventing CisPt-induced nephrotoxicity remains nowadays a real problem for the oncologist, and the ideal renoprotective

agent is still to be discovered. Until now, several attempts made at preserving the kidneys—in addition to hydration protocols—during CisPt treatments did not result in satisfactory outcomes [27]. While waiting for less nephrotoxic compounds and more effective nephroprotection procedures, the clinician must be aware of available prevention strategies, relying on a tryptic basis: drug dosage adjustment, screening for renal markers of early tubulotoxicity and pretreatment clinical evaluation. From our point of view, these three aspects are the keys for an effective onco-nephrological approach of each cancer patient eligible for CisPt chemotherapy.

This study confirms the need for a better kidney function monitoring during chemotherapy cycles, not only based on Pcr, but also with the help of validated biomarkers. This improved monitoring should be conducted before (for baseline evaluation), during and after each cycle, and might trigger alerts of RPTECs injuries more rapidly, which in some patients would otherwise remain undetected. The identification of subclinical renal lesions and/or proven AKI would undoubtedly lead clinicians to consider adapting the ongoing treatment and further chemotherapy cycles.

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Conflict of interest statement

None declared.

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