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Cisplatin nephrotoxicity aggravated by cardiovascular disease and diabetes in lung cancer patients

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ABSTRACT: Ageing lung cancer patients may be at increased risk of Cisplatin (Cp) nephrotoxicity, because of comorbidities leading to accelerated ageing of the kidneys. Therefore, the Cp-induced impairement of renal function was compared between no comorbidity (NC) and hypertension plus ischaemic heart disease (CD) patients or others having diabetes mellitus plus ischaemic heart disease (DMIH).

In a preliminary study, glomerular filtration rate (GFR) was measured by clearance of technetium 99m-labelled diethylene-thiamine penta-acetate in 38 lung cancer patients with normal serum creatinine concentration ([creat]). Then, the incidence of nephrotoxicity was analysed retrospectively over 1st–4th cycles of Cp treatment among 242 lung cancer patients with initially normal [creat]. GFR was repeatedly estimated using calculated creatinine clearance.

Pre-treatment GFR was 57 ± 3 mL·min^{-1}·m^{-2} in those with normal (n=15) and 42 ± 2 mL·min^{-1}·m^{-2} in those with pathologically increased (n=23) [creat] any time following their 2nd–4th Cp cycle ($p<0.05$). The retrospective analysis revealed that Cp-induced nephrotoxicity developed in 7.5% of the NC (n=80), in 20.9% of the CD (n=110) and in 30.8% of the DMIH (n=52) subgroups. Within the overall dropout rate from further Cp chemotherapy, nephrotoxicity was responsible in 14% of NC, 38% in CD and 75% in DMIH patients.

A major portion of our ageing lung cancer patients suffered from comorbidities leading to reduced renal resistance to Cp nephrotoxicity.

KEYWORDS: Ageing kidney, cardiovascular disease, cisplatin nephrotoxicity, diabetes mellitus, lung cancer

High-dose cisplatin (Cp)-based combination chemotherapy regimens are used as front-line treatments of nonsmall cell and small cell lung cancer [1]. The therapeutic effects of Cp are significantly improved by dose escalation. However, high-dose therapy with Cp is limited by its cumulative nephrotoxicity [2]. Cp is toxic to the renal proximal and distal tubules [3]. Different hydration (saline infusion) protocols were developed that reduced nephrotoxicity and allowed dose escalation to therapeutic levels [4]. However, even with vigilant hydration, approximately one-third of patients treated with Cp have transient elevation of blood urea nitrogen levels or other evidence of kidney damage in the days following Cp treatment [5]. According to BERNS and FORD [6], ~20% of acute renal failure cases among hospitalised patients are due to Cp nephrotoxicity. DE JONGH *et al.* [7] analysed prognostic factors for nephrotoxicity of high-dose Cp in 400 patients with a median age of 54 yrs and suffering from different solid tumours. Nephrotoxicity was defined as a $\geqslant$25% decline of estimated creatinine clearance (C_{creat}) at any time during the evaluation period. 29% of patients developed nephrotoxicity, but temporary elevation of serum creatinine concentration ([creat]) above the upper normal limit was observed in 41% of patients. Their multivariate analysis selected age, female sex, smoking, paclitaxel coadministration and hypoalbuminaemia as independent risk factors of Cp-induced decrease of renal function.

In developed countries, lung cancer patients have a median age of 70 yrs [8]. Notably, the ageing

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kidney may be more susceptible to nephrotoxins [9]. Ageing people are affected by comorbidities as, for example, hypertension plus ischaemic heart disease (CD) and/or diabetes mellitus plus ischaemic heart disease (DMIH). Underlying and undiagnosed, early-stage nephrosclerosis induced by age, CD, or diabetes mellitus alone or in combination may be present among older patients who receive antihypertensive, vasodilatator or antidiabetic treatment but have no elevation of [creat]. However, in aged cancer patients [creat] and the concentration of urea may be only pseudonormal because of decreased muscle mass and protein intake, respectively. In conditions with reduced production of creatinine and low [creat], abnormally low glomerular filtration rate (GFR) may occur for extended periods before [creat] will reach the upper limit of the reference range [10]. Increased [creat] is to be considered the least sensitive indicator of reduced GFR [10]. Still, based on normal serum indices of renal function, aged CD or DMIH patients may receive full-dose Cp treatment for lung cancer. LAUNAY-VACHER *et al.* [11] have reported that, before chemotherapy, ~60% of 445 lung cancer patients had unrecognised, stage 2 kidney disease (GFR 60–89 mL·min^{-1}), as estimated by C_{creat}.

Therefore, in order to determine the occurrence of high-dose Cp nephrotoxicity in lung cancer patients, [creat], clearance of technetium 99m-labelled diethylene-thiamine penta-acetate (^{99m}Tc-DPTA) (GFR) and C_{creat} (estimated GFR; eGFR) were compared before and after the administration of Cp in patients suffering also from CD, DMIH or being free from these underlying comorbidities (no comorbidity; NC).

MATERIAL AND METHODS

Study subjects and design

The Pulmo-Oncology Unit of the Dept of Pulmonology at Semmelweis University (Budapest, Hungary) treats 250–300 nonsmall and small cell lung cancer patients annually. Since Cp-induced reversible or persistent uraemia was estimated to occur in ~30% of our patients, in order to investigate whether GFR was already reduced before Cp treatment when [creat] was still normal, in a preliminary prospective study, we measured GFR by clearance of ^{99m}Tc-DPTA in 38 stage IIIB–IV lung cancer patients with normal [creat] scheduled for Cp-based chemotherapy. ^{99m}Tc-DPTA clearance was measured at the Dept of Radiology and Oncotherapy of Semmelweis University by the same investigator (L. Duffek). ^{99m}Tc-DPTA (Izotóp Intézet Kft., Budapest, Hungary) was administered *i.v.* at a dose of 40 MBq. Patients were then grouped according to their highest post-Cp [creat] either below (n=15) or above (n=23) the upper limit of the reference range (>106 μmol·L^{-1}) any time during their chemotherapy (2–4 cycles). Cp was administered at 75 mg·m^{-2} *i.v.* in each cycle. Cp infusions were ⩾21 days apart.

Next, we retrospectively analysed records of patients (n=242) suffering from stage IIIA–IV nonsmall or small cell lung cancer and receiving chemotherapy between January and December 2006. High-dose Cp therapy was indicated by our oncology team and, in addition to fulfilment of many other criteria, Cp was recommended only for patients with normal [creat] and urea concentration and without any other apparent symptoms or signs of altered renal function. Based on initial evaluation of the 242 patients, three major subgroups were formed according the absence or presence of the comorbidities CD and/or DMIH. The NC subgroup had no hypertension, ischaemic heart disease or diabetes mellitus. The CD subgroup was formed based on the presence of long-term, medically controlled hypertension and ischaemic heart disease (together cardiovascular disease; n=110), and the DMIH subgroup was based on the combined presence of diabetes mellitus and ischaemic heart disease without hypertension (n=52). The diagnosis of chronic arterial hypertension was based on history and the use of antihypertensive medications. Ischaemic heart disease was diagnosed based on history, ECG abnormalities and previous treatment with coronary vasodilators, platelet aggregation inhibitors or percutaneous transluminal coronary angioplasty. None of the CD patients suffered from uncontrolled hypertension, angina pectoris, acute myocardial infarction or cardiac decompensation, or from any other acute or severe cardiovascular comorbidity that could have contraindicated chemotherapy with high-dose Cp. Diabetes mellitus was diagnosed based on history, treatment with insulin (n=5) or oral antidiabetetic treatment (n=47) and higher than normal fasting serum glucose concentration. None of the DMIH patients suffered from uncontrolled hyperglycaemia or had symptoms of major complications of diabetes. Urinary protein test showed opalescence (⩾1 g·day^{-1}) in two patients and slight opalescence (0.5–1.0 g·day^{-1}) in two other patients; the majority had negative (<0.5 g·day^{-1}) results. Patients received several subsequent combined chemotherapy courses, always containing high-dose Cp (75 mg·m^{-2} *i.v.*), and each pre- and the highest post-Cp [creat] and urea concentration values were recorded. Cp-induced persistent uraemia (which indicates Cp nephrotoxicity) was a frequent cause of exclusion from further Cp treatment. The number of these patients was compared between the three groups. Clinical data, such as age, sex, chronic comorbidity, blood pressure and stage of lung cancer were collected. With regard to laboratory data, serum glucose, [creat] and urea concentrations were analysed. [creat] was determined based on the modified Jaffe two-point kinetic reaction using commercially available test from Dialab (Wiener Neudorf, Austria). C_{creat} (eGFR) was calculated according the Cockcroft–Gault equation [12]. This calculation was selected because the mean age of our patients was <65 yrs [13].

Other treatments and drugs

Cp was provided by Teva Hungary (Budapest, Hungary) and EBEWE Pharma (Unterach, Austria) and administered at a dose of 75 mg·m^{-2}. One of three additional chemotherapeutic agents were given in combination with Cp: gemcitabine (1,250 mg·m^{-2}; Eli Lilly, Houten, the Netherlands), etoposide (3×120 mg·m^{-2}) and paclitaxel (175 mg·m^{-2}; both Bristol-Myers Squibb, Princeton, NJ, USA). Neutropenia was treated with granulocyte colony-stimulating factor (filgrastim, 48 mU; Amgen, Breda, the Netherlands), severe thrombocytopenia with platelet transfusion, and anaemia with erythropoietin (Epoetin alfa, 40,000 IU·week^{-1}; Janssen-Cilag, Centocor, Leiden, the Netherlands) and/or transfusion as indicated. Patients received antinociceptive and antiemetic drugs, bisphosphonate, methylprednisolone and other symptom relievers, as needed.

Hydration protocol

An *i.v.* infusion of 500 mL 0.9% NaCl was followed by either gemcitabine, taxol or etoposide in a further 500 mL saline.

TABLE 1 Pre-cisplatin (Cp) glomerular filtration rate (GFR) of 38 initially nonuraemic lung cancer patients

Subgroup	Patients	[creat] μmol·L^{-1}		Pre-Cp GFR mL·min^{-1}·m^{-2}	Age yrs	Males/females
		Pre-Cp	Post-Cp			
Cp nephrotoxicity	23	79±4$^{*,\#}$	167±12$^{*,\#}$	42.4±2.3$^{*,\#}$	63.6±1.5$^{\#,\P}$	13/10$^{\P,+}$
No Cp nephrotoxicity	15	68±3	87±4	56.9±2.7	60.5±2.8	8/7

Data are presented as n or mean±SEM. [creat]: serum creatinine concentration. $^{\#}$: unpaired t-test; ¶: not significant ($p>0.05$); $^{+}$: Fisher's exact test. *: $p<0.05$ compared with no Cp nephrotoxicity.

After a third 500-mL saline infusion, Cp was infused again in 500 mL. In our hands, infusion of 500 mL usually takes 20–30 min. Following Cp, the fifth 500 mL saline was infused (total volume of saline 2,500 mL within ~2.5 h) and the infusion treatment was ended with 100 mL 20% mannitol (Baxter, Deerfield, IL, USA) *i.v.*; methylprednisolone (40 mg) and various antiemetic drugs were also given in many patients.

Statistical analysis

Data are presented as means±SEM. Statistical analysis was performed using GraphPad software (Graph Pad Prism 5.0; Graph Pad Software, Inc., San Diego, CA, USA) using Fisher's exact test, the Chi-squared test and t-tests (paired and unpaired) as appropriate. One-or two-way ANOVA and the Kruskal–Wallis test was used to compared more than two groups. Normally distributed data were analysed by ANOVA and non-Gaussian distributed or nonparametric values were analysed by Kruskal–Wallis test. After one-way ANOVA, if significant difference ($p<0.05$) was found, the Newman–Keuls multiple comparison *post hoc* test was used for further analysis. After two-way ANOVA, a Bonferroni post-test was used. After the Kruskal–Wallis test, Dunn's multiple comparison *post hoc* test was performed. The applied tests are described in the table and figure legends.

RESULTS

Out of the 38 lung cancer patients, 23 patients responded with pathologically increased [creat] after Cp (table 1), although pre-treatment [creat] values were normal in both groups. Pre-treatment GFR, as measured by clearance of ^{99m}Tc-DPTA, was significantly reduced by ~25% in those lung cancer patients with azotaemia who responded to 2–4 cycles of Cp treatment.

To confirm this preliminary observation, a restrospective analysis of Cp nephrotoxicity in 242 lung cancer patients treated with Cp was performed. About two-thirds of them suffered from major comorbidities like CD or DMIH (table 2). No differences were noted in the distribution of sex, Cp dose or in the ratio of patients receiving any of the other chemotherapeutics. Blood pressure and cardiac frequency were also similar in the three subgroups, indicating good blood pressure control in the CD subgroup.

The number of patients made it possible to analyse four subsequent Cp cycles. After the first Cp treatment, [creat] increased in all subgroups, but the change was significantly greater in subgroups CD and DMIH than NC (both $p<0.05$; table 3). The second Cp dose could be given to fewer patients than the first in all three subgroups, because of Cp nephrotoxicity in many cases (see later). Although pre-Cp [creat] values were again in the reference range, the second Cp infusion induced a larger increase in [creat] than the first one. This time, concentrations entered the pathological range in the DMIH group and were close to it in the CD, but not the NC, subgroup. The 3rd Cp cycle was administered in only ~50% of the patients initially treated. Pre-Cp [creat] was again normal, but post-Cp values increased into the pathological range in the CD and DMIH, but not the NC, subgroups. Most patients who developed azotaemia after the 3rd Cp administration demonstrated normalised [creat] after a few weeks; only a few of them dropped out at this stage. The 4th high-dose Cp treatment was given to patients with normal [creat] values, but again, those in the CD and DMIH subgroups developed azotaemia, which was not observed in the NC subgroup (table 3). Serum urea concentrations followed a similar pattern to [creat] (data not shown).

Figure 1 shows that Cp-induced persistent azotaemia (Cp nephrotoxicity) developed in 7.5% of NC, 20.9% of CD ($p<0.05$ compared with NC) and in 30.8% of DMIH ($p<0.01$ compared with NC) patients. When the contribution of nephrotoxicity to overall dropout from further Cp chemotherapy was examined, the ratio was 14% in NC, 38% in CD ($p<0.01$ compared with NC) and 75% in DMIH ($p<0.0001$ compared with NC and $p<0.01$ compared with CD) patients.

Figure 2 demonstrates eGFRs of those patients who remained treatable with Cp before and after the 1st–4th cycles. Pre-Cp values moderately and successively decreased after Cp cycles but remained comparable in the three groups throughout the 1st–4th cycles. It seemed that eGFR calculated by the Cockcroft–Gault equation was not sensitive enough in predicting higher vulnerability of the kidney in CD or DMIH patients. However, relative to the Cp-naïve values, eGFR before the 4th Cp cycle was diminished by only ~4% in NC, but 16 and 18% in CD and DMIH groups, respectively. Overall, post-Cp eGFRs followed an inverse pattern relative to [creat] values. NC patients responded with significantly reduced eGFR only after the 1st cycle, while the two comorbid groups had reduced eGFP in all cycles of Cp. Statistical analysis indicated that eGFR was more reduced ($p<0.05$) in CD and DMIH *versus* NC patients after the 2nd cycle.

DISCUSSION

The present study shows that: 1) CD and/or DMIH are frequent among lung cancer patients; 2) these comorbidities

TABLE 2 Clinical data of patients receiving high-dose cisplatin (Cp) for lung cancer

Characteristic	NC	CD	DMIH
Patients n	80	110	52
Age yrs	56±1	60±1$^{*,\#}$	62±1$^{\#,\P}$
Males/females n	45/35	66/44$^{\P,+}$	33/19$^{\P,+}$
BMI kg·m^{-2}	24.3±0.4	25.4±0.4$^{\#,\P}$	25.4±0.6$^{\#,\P}$
Dose of Cp per treatment mg	123±2	126±2¶,§	124±4¶,§
Total dose of Cp mg	375±22	399±22$^{\#,\P}$	392±43$^{\#,\P}$
Mean number of cycles n	3.1±0.2	3.2±0.2$^{\P,+}$	3.2±0.3¶,§
Patients receiving gemcitabine/etoposide/taxol n	38/41/1	52/55/3^{¶,f}	25/24/3^{¶,f}
Systolic/diastolic blood pressure mmHg	132±2/81±1	134±2/81±1$^{\#,\P}$	137±3/84±2$^{\#,\P}$
cardiac frequency beats·min^{-1}	81±1	82±1$^{\#,\P}$	86±2$^{\#,\P}$

Data are presented as mean±SEM, unless otherwise stated. NC: no comorbidity; CD: hypertension and ischaemic heart disease; DMIH: diabetes mellitus and ischaemic heart disease; BMI: body mass index. $^{\#}$: ANOVA with Newman–Keuls multiple comparison *post hoc* test; ¶: not significant compared with NC ($p>0.05$); $^{+}$: Fisher's exact test; §: Kruskal–Wallis test with Dunn's multiple comparison *post hoc* test; ^{f}: Chi-squared test. *: $p<0.05$ compared with NC.

predispose patients to Cp nephrotoxicity, while those elderly persons who are free from CD and DMIH are quite resistant to the renal side-effects of Cp; and 3) development of post-Cp uraemia seems to be predictable by a moderate, but significant, reduction of GFR, as estimated by calculated C_{creat} or measurement of ^{99m}Tc-DPTA clearance. Although it has been known that serum markers of renal function remain in the reference range when there has already been a decline of GFR [10], the present observations indicate that especially in patients suffering from CD or DMIH, normal [creat] misguides about the state of renal function or predictable renal tolerance towards the toxic effects of high-dose Cp. Estimation of C_{creat} might provide more valuable information and predict more reliably the risk of nephrotoxicity.

TABLE 3 Serum creatinine concentrations ([creat]) in lung cancer patients receiving 1–4 cycles of high-dose cisplatin (Cp) chemotherapy for lung cancer

Cp cycle	NC	CD	DMIH
1st			
Patients	80	110	52
[creat] μmol·L^{-1}			
Pre-Cp	77±1	78±1$^{\#}$	77±3$^{\#}$
Post-Cp	82±2*	95±4*,¶	94±4*,¶
2nd			
Patients	68	96	49
[creat] μmol·L^{-1}			
Pre-Cp	80±2	86±2$^{\#}$	82±3$^{\#}$
Post-Cp	88±4*	105±5*¶	110±6*,¶
3rd			
Patients	42	64	31
[creat] μmol·L^{-1}			
Pre-Cp	85±3	91±3$^{\#}$	83±4$^{\#}$
Post-Cp	91±5*	113±5*,¶	117±9*,¶
4th			
Patients	35	47	30
[creat] μmol·L^{-1}			
Pre-Cp	84±4	95±3^{ns}	89±3$^{\#}$
Post-Cp	93±5*	117±8$^{*\#}$	121±5*,¶

Data are presented as n or mean±SEM. NC: no comorbidity; CD: hypertension and ischaemic heart disease; DMIH: diabetes mellitus and ischaemic heart disease. *: $p<0.05$ compared with pre-Cp (paired t-test); $^{\#}$: not significant compared with NC (two-way ANOVA with Bonferroni after test); ¶: $p<0.05$ compared with NC (two-way ANOVA with Bonferroni after test).

Advanced age, CD or diabetes mellitus and, especially, their combination may increase the sensitivity of the kidney to the above toxic effects of Cp. Ageing is associated with glomerulosclerosis and arteriosclerosis of intrarenal vessels, leading to loss of functional nephrons [9]. Renal blood flow and GFR are reduced, and many of the normal renal tubular absorption and secretion abilities are blunted. SILVA [9] suggested that ageing

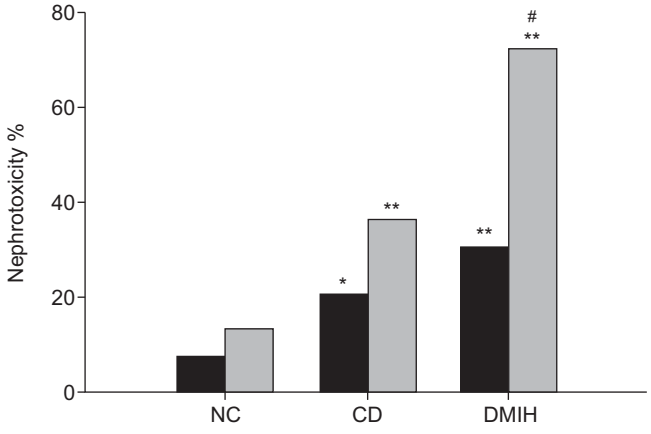

FIGURE 1. Frequency of nephrotoxicity (■) and nephrotoxicity-related drop-out from further cisplatin (Cp) treatment (■) in lung cancer patients receiving 1–4 cycles of high-dose Cp and suffering from hypertension and ischaemic heart disease (CD), or diabetes mellitus and ischaemic heart disease (DMIH), or being free from these severe comorbidities (NC). *: $p<0.05$ compared with NC; **: $p<0.01$ compared with NC; $^{\#}$: $p<0.01$ compared with CD (two-tailed difference tests).

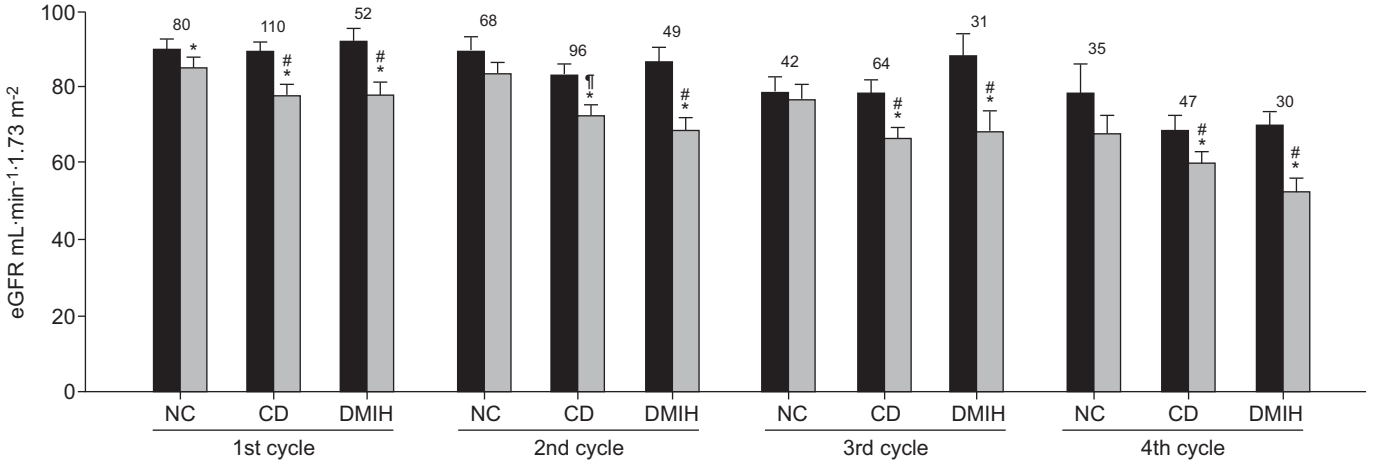

FIGURE 2. Pre- (■) and post-cisplatin (Cp) (■) estimated glomerular filtration rate (eGFR) values during the 1st–4th cycles of high-dose Cp treatments in lung cancer patients suffering from no comorbidity (NC), controlled hypertension and ischaemic heart disease (CD), or controlled diabetes mellitus and ischaemic heart disease (DMIH). Numbers above the bars represent the number of patients. *: $p<0.05$ compared with pre-Cp (paired t-test); ¶: $p<0.05$ comapared with NC (two-way ANOVA with Bonferroni after test); ¶: not significant compared with NC (two-way ANOVA with Bonferroni after test).

should be seen as the erosion of generous spare capacity or loss of renal safety margins. The tubular systems becomes less capable of conserving or excreting NaCl [14]. Among the elderly, exsiccation and/or hyponatraemia becomes prevalent [15]. In the ageing kidney, the number and volume of tubules are reduced, and the volume of the renal interstitium increases due to fibrosis, which may be associated with inflammation [16]. Intrarenal arterial sclerosis is noted with increased frequency in patients aged 10–19, 20–39, 40–64 and >65 yrs [17]. Important details have been uncovered regarding the physiological mechanisms of kidney ageing, such as glomerular capillary hypertension, glomerulosclerosis, reduced number of nephrons and NO deficiency [18, 19]. Ageing induces increased renal synthesis of reactive oxygen species [20] and advanced glycation end products [21]. Biomarkers of senescence, such as acute-phase proteins, accumulate in the aged kidney [22].

Chronic systemic hypertension [23] and diabetes mellitus [24, 25] accelerate ageing of the kidney. OHTA *et al.* [26] demonstrated higher pulse-wave velocity, a sign of atherosclerosis, in main renal arteries and the renal interlobar arteries of middle-aged patients suffering from hypertension and diabetes mellitus. Hypertensive nephrosclerosis is associated with chronic ischaemic damage to the tubulointerstitium [27], the major target of Cp nephrotoxicity. In addition to physiological ageing, intrarenal arterial sclerosis is accelerated by long-term hypertension and diabetes mellitus [18]. Diabetes mellitus is complicated with early renal function decline [24, 25]. As a result of all these, the course of other primary renal diseases (glomerulonephritis, acute renal failure and endotoxin-induced thrombosis) become accelerated [28, 29]. Accordingly, the development of azotaemia following high-dose Cp administration may betray underlying renal disease induced by CD or diabetes mellitus.

Based on these data, it is not surprising that nephrotoxicity of high-dose Cp was exaggerated in aged lung cancer patients suffering from CD or DMIH. Underlying DMIH was associated with the greatest frequency of azotaemia following high-dose Cp. Since none of our patients developed acute or chronic renal failure, or needed renal replacement therapy, one could ask: is this moderately severe renal side-effect of Cp so important clinically, once life expectancy of lung cancer patients is unfavourable anyway? The issue of Cp-induced uraemia is very important, because: 1) during subsequent chemotherapy cycles, lower dose or no Cp will be administered; and 2) the Cp-induced glomerulotubular imbalance results in enhanced urinary loss of Mg^{2+}, Ca^{2+}, K^+, Na^+, Cl^- and water. These effects on electrolyte and water homeostasis may induce cardiac arrhythmia, circulatory shock and death.

There is a long list of agents which may ameliorate the nephrotoxicity of Cp in experimental animals [30]. The US Food and Drug Administration has approved the organic thiophosphate amifostine (Ethyol) for use in patients receiving Cp [30, 31]. Reported efficacy of this tissue cytoprotector in cancer patients is not unequivocal [32] and the drug is expensive. The only available preventive measure of universally proven efficacy is hyperhydration by isotonic saline before, during and after the infusion of Cp [4]. To our knowledge, there has been no hydration protocol accepted and followed universally in lung cancer patients. The critical events seem to occur almost immediately (within a few hours) after Cp administration [33]. Therefore, protective measures should be applied before, during and immediately after Cp infusion [33]. There have been no prospective, randomised studies for finding out what is appropriate hydration around Cp infusion in elderly people with underlying subclinical renal disease [34]. Companies manufacturing Cp recommend pre-Cp hydration enough to induce 100–200 $mL \cdot h^{-1}$ (2,400–4,800 $mL \cdot day^{-1}$) saline diuresis by the time of Cp infusion, but the recommended volume, velocity and timing of *i.v.* saline infusion before, during and after Cp seem not to be optimal for reaching the above goal. Although salt loading is more important than hydration [35], the exact definition of saline diuresis has not been detailed either. We define it as voiding urine of ~1% NaCl concentration. Saline infusion, in contrast

to water loading, is only slowly followed by saline diuresis. An interval of 1 h after the start of 0.9% NaCl infusion (1,000 mL) is probably insufficient for induction of saline diuresis. Notably, high urine flow (water diuresis) alone is not renoprotective against Cp [36]; furthermore, the antitumour efficacy of Cp may be reduced by water loading [36]. Healthy adults consuming a Western diet with conventional salt intake (~3 $g \cdot day^{-1}$) void 1,000–1,500 mL urine over 24 h and their urinary NaCl concentration is <0.4% [37]. Based on these estimations, saline diuresis of a healthy adult may be no greater than ~50 $mL \cdot h^{-1}$. Aged and anorexic cancer patients probably do have markedly reduced urinary saline excretion, which might never have been systematically tested. Diuretics administered for hypertension or other common reasons in elderly people may make these patients even more exsiccated at the time they arrive for chemotherapy (early morning). OZOLS *et al.* [38], and TOWNSEND and HANIGAN [39] administered a total volume of 6 L saline during a day of Cp administration. DE JONGH *et al.* [7] infused first 1 L 0.9% NaCl, then Cp in 250 mL hypertonic (3%) NaCl over ⩾3 h, followed by 2 L 0.9% NaCl (~6 h total treatment time). In 2006, in our department (Dept of Pulmonology, Semmelweis University), high-dose Cp was infused in 500 mL 0.9% saline (over ~30 min) after prior infusion of 1 L 0.9% NaCl (~1 h). Patients then received a further 1.0–1.5 L NaCl and 100 mL 20% mannitol after Cp. The total infused volume was around 3–4 L and administered within 3–4 L. Thus, it seems we may have provided weaker pre-Cp hydration, administered Cp more quickly and, certainly, we have never controlled urinary volume or urinary Na^+ concentration (saline diuresis) any time before, during or after Cp administration. The administration of mannitol has also been somewhat contradictory, since this agent might also have worsened pre-existing renal dysfunction [40].

According to HANIGAN *et al.* [41], the infusion of saline protects kidney cells by increasing the osmolality, rather than the concentration, of Na^+ or Cl^-. These authors have documented that the *in vitro* toxicity of Cp in cultured proximal tubular cells could be equally prevented by increasing the osmolality of the medium with mannitol, sucrose, sodium gluconate or NaCl. Cp was toxic in hypo-osmolar media (~220 $mOsm \cdot kg^{-1}$), but high–normal osmolality (~280 $mOsm \cdot kg^{-1}$) provided nearly full protection. It has been hypothesised that the change in osmolality induces a change in cell and nuclear volume, and a consequent change in chromatin structure, which reduces the accessability of Cp to DNA. It is also considered possible that the renal cellular metabolism of Cp, which increases its toxicity, is altered by increased osmolality.

In 2008, the European Society of Clinical Pharmacy Special Interest Group on Cancer Care formulated clear recommendations on the prevention of Cp nephrotoxicity [42]. The cornerstones of the recommendations are: 1) the estimation of GFR or C_{creat} using the abbreviated Modified Diet in Renal Disease or the Cockcroft–Gault equation; 2) maintenance or induction of euvolaemia before, during and after Cp; 3) the slow administration of Cp; 4) the maintenance of 3–4 $L \cdot day^{-1}$ saline diuresis during the preceding day and 2–3 days after Cp; and 5) avoidance of diuretics, including furosemide and mannitol.

In conclusion, before starting high-dose Cp chemotherapy in lung cancer patients, the risk of nephrotoxicity should always be evaluated based on eGFR [42] and coexisting CD or DMIH, because these conditions narrow the tolerance of the kidneys to Cp. The 2008 recommendations of the European Society of Clinical Pharmacy Special Interest Group on Cancer Care on the prevention of Cp nephrotoxicity [42] should also be followed regarding hydration using physiological saline before, during and after Cp administration in aged, multimorbid lung cancer patients. However, vigourous saline infusion of CD and DMIH patients may lead to volume overload and pulmonary oedema. Further studies are needed for finding out how to effectively prevent Cp nephrotoxicity without the risk of cardiac overload.

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STATEMENT OF INTEREST

None declared.

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