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Pre-treatment risk factors to predict early cisplatin-related nephrotoxicity in locally advanced head and neck cancer patients treated with chemoradiation: A single Institution experience

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ABSTRACT

Objectives: Cisplatin is essential in the curative treatment of locally advanced head and neck squamous cell carcinoma (LA-HNSCC) patients. The assessment of risk factors to predict an early cisplatin-induced nephrotoxicity could help in better managing one of the most relevant cisplatin-related dose-limiting factors.
Material and methods: We retrospectively collected data of LA-HNSCC patients treated at our Institution from 2008 to 2019. Patients received cisplatin in a curative setting concurrently with radiation. Acute Kidney Injury (AKI) was assessed as a dichotomous variable (CreaIncr) based on pre-treatment values, and values recorded at days 6–20 post-first cycle of cisplatin. Univariable logistic regression models were performed to investigate associations between CreaIncr and clinical characteristics. A multivariable logistic model on a priori selected putative covariates was performed.
Results: Of the 350 LA-HNSCC treated patients, 204 were analyzed. Ninety (44 %) suffered from any grade AKI (grade I 51.1 %): out of them, 84.4 % received high-dose cisplatin (100 mg/m2 q21). On the univariable logistic regression model, male sex, age, serum uric acid, creatinine, concomitant drugs, and cisplatin schedule were significantly associated with a higher rate of AKI. At multivariable model, age ($p = 0.034$), baseline creatinine ($p = 0.027$), concomitant drugs ($p = 0.043$), and cisplatin schedule (one-day bolus or fractionated high-dose vs. weekly; $p = 0.001$) maintained their significant association.
Conclusions: Identifying pre-treatment risk factors in LA-HNSCC patients may improve decision-making in a setting where cisplatin has a curative significance. A strict monitoring of AKI could avoid cisplatin dose adjustments, interruptions, and treatment delays, thus limiting a negative impact on outcomes.

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Introduction

Background

Cisplatin is currently used in clinical practice among different cancer types, including head and neck squamous cell carcinoma (HNSCC), where it remains a gold standard, both in the curative and palliative settings.

Four large randomized phase III trials in locally advanced (LA) HNSCC have shown better loco-regional control and overall survival (OS) with three-weekly high-dose intravenous CDDP (100 mg/m^2) given concurrently with external beam radiotherapy (RT) compared with radiotherapy alone [1–4]. In this context, higher cumulative cisplatin doses are associated to better survival rates independently of the schedule of chemotherapy administration [5]. However, 64–71 % of LA-HNSCC patients receive the full planned dose of cisplatin during radiotherapy [6]. Therefore, an accurate patient selection is essential to avoid or early detect a treatment-related renal damage in order to guarantee an optimal cisplatin dose intensity.

In a specific cohort of HNSCC patients treated with three-weekly cisplatin (at 100 mg/m^2 dose) concomitantly to RT, C-AKI occurred in 69 % of patients. In this setting, arterial hypertension, chemotherapy-nausea and vomiting were significantly associated with C-AKI [7]. In the last years, there has been increasingly emerging high-quality evidence that chemo-radiotherapy (CRT) with three-weekly cisplatin is more nephrotoxic than once-weekly cisplatin in curative-intent management of LA-HNSCC [6,8–10]. A systematic review and *meta*-analysis of prospective trials clearly showed that kidney damage was significantly higher with three-weekly cisplatin with respect to severe (grade 3–4) nephrotoxicity (5 % vs. 1 %, p = 0.0099) in the definitive setting [6]. Even in post-operative high-risk LA-SCCHN patients randomly assigned either with 3-weekly cisplatin (100 mg/m^2) or with weekly cisplatin (40 mg/m^2), a more recent multi-institutional phase II/III trial confirms that renal impairment of any grade was much less frequent in once-weekly arm (30 % vs. 40 %) [10]. Supplementary analyses of this clinical trial showed that the development of an acute kidney injury within 30 days after the completion of CRT is an independent negative prognostic factor, especially in patients treated with a three-weekly schedule [11].

The first paper describing the prevention of renal damage by hydration was published in 1977 [12]. Even though nowadays we know that cisplatin is excreted through kidneys, and can accumulate in the proximal tubules, evidence-based recommendations on specific hydration regimens and supplementation strategies are limited [13].

Given this background, we conducted a retrospective analysis of LA-HNSCC patients treated with curative intent by cisplatin-based CRT. Our aim was to evaluate baseline factors that could be related to C-AKI occurrence.

Methods

We retrospectively collected data of histologically confirmed LA-HNSCC patients treated with cisplatin and radiotherapy between 2008 and 2019 at our Institution, a tertiary cancer center in Italy.

The study was approved by the institutional Ethical Committee on the 28th March 2019 (INT 58/19). Written informed consent for participation was not required for this study in accordance with national legislation and institutional requirements.

Subjects were defined cisplatin-eligible given that all these conditions were met prior to CRT start [14]: estimated glomerular filtration rate (eGFR) $\geq$ 60 ml/min, absence of pre-existing moderate/severe peripheral neuropathies, hearing loss, and heart failure. All patients were treated with CDDP in a curative setting - used at 100 mg/m^2 every three weeks or weekly at 50 mg/m^2 dose - concurrently with radiation (CRT). Cisplatin was administered in a single infusion or fractionated infusions over consecutive days; in case of fractionation, we considered the cumulative cisplatin dose (mg/m^2) administered. We included patients $\geq$ 18 years of age with available baseline blood exams (day before treatment initiation) and at least one blood measurement within 6–20 days after the first CDDP course. This timing was selected to identify any early treatment-related creatinine increased (CreaIncr) before reaching the expected second cycle of concomitant chemotherapy. Prior to antiemetic prophylaxis and CDDP administration, all patients received 500 ml of saline with magnesium sulphate supplementation (8 mEq in case of normal magnesium blood levels, higher doses in case of pre-existing hypomagnesemia). After cisplatin administration, all patients received intravenous hydration for at least 12 h or 36 h, based on the chemotherapy schedule (weekly or every three weeks, respectively). In all cases, lab tests were assessed at least weekly until 30 days after the conclusion of CRT. In patients receiving high-dose CDDP, lab test were assessed 24 h after each chemotherapy administration to detect any early kidney injury or electrolyte imbalance, which were corrected accordingly.

We collected data for potential predictors of nephrotoxicity on the basis of the available literature on cisplatin-related toxicity. The following parameters were retrieved from clinical charts: age, sex, comorbidities, concomitant medications (diuretics, anti-hypertensive drugs, statins, cardiovascular drugs, non-steroidal anti-inflammatory drugs-NSAIDs, proton-pump inhibitors), body mass index (BMI), body surface area (BSA); baseline blood exams, including creatinine, creatinine clearance, blood urea nitrogen, serum uric acid, magnesium, albumin. Clinical information included CDDP dose (mg/m^2), regimen and schedule of administration, and date of infusions. Data on early termination of CDDP or shift to other platinum salts (notably carboplatin) were also evaluated. Exclusion criteria included missing baseline and/or during follow-up of blood exams.

Acute Kidney Injury (AKI) was assessed as a dichotomous variable (CreaIncr) based on baseline values and values recorded at days 6–20 post-first cycle of CDDP (Yes = Grade > 0 vs. No = Grade0); AKI was defined according to KDIGO clinical practice guidelines [15], and staged according to severity using the latest classification system available at the time of data collection (version 4.0 of the Common Terminology Criteria for Adverse Events - CTCAE).

The long-term renal outcome was assessed by collecting the latest creatinine value until the ninetieth day after the conclusion of CRT. We compared the frequency of patients without (CTCAE grade = 0) vs. with any grade (CTCAE grade $\geq$ 1) creatinine increase stratifying according to the occurrence of CreaIncr. The small number of CTCAE grade $\geq$ 3 creatinine increase events (occurred in 2 patients) did not let us compare patients with or without CreaIncr developing a severe vs. a mild chronic renal failure.

Statistical methods

Patient and disease characteristics and treatments are summarized overall and by creatinine increase (yes, no). The standardized mean difference (SMD) was used as a measure of between-group differences [16]. SMD is considered to indicate a possible between-group imbalance at a value of around 0.3. For SMD values of 0.3 and above it is important to assess the clinical or practical importance of such differences.

Univariable logistic regression models were performed to investigate associations between CreaIncr and clinic-pathologic characteristics including blood exams, comorbidities, number of concomitant drugs (including angiotensin-converting enzyme, angiotensin blockers, calcium-blockers, and NSAIDs), treatment (Concomitant and induction, Concomitant), schedule of CDDP administration (Weekly, One-day bolus, 2–3 days fractioning), body mass index, body surface area, and age. A multivariable logistic model on *a priori* selected putative covariates including sex, age, hypertension, diabetes, BMI, serum uric acid, magnesium, albumin, creatinine and its clearance (CrCl) at baseline, number of concomitant drugs, treatment, and schedule of CDDP administration was performed. In all models, continuous variables were

modeled using 3-knots restricted cubic splines [17].

Contingency tables were analyzed with Fisher's exact test or chi squared test, as appropriate. Statistical analyses were performed with SAS™ (SAS Institute, Cary, NC) and R software (R Foundation for Statistical Computing, Vienna, Austria). P-value ≤ 0.05 was considered statistically significant.

Results

From January 2008 to December 2019, 350 HNSCC patients were treated in a curative setting at our Institution. Among those patients, 146 patients were excluded due to: missing baseline blood exams, missing blood exams during the follow-up, and treatment with carboplatin or cetuximab concurrently to RT (Figure 1).

Baseline clinical characteristics are summarized in Table 1. The majority of patients were male (74 %), with a median (1st and 3rd quartile) age of 56 years (51–63). The main tumor subsite was oropharynx (65.7 %; 74 % of them had a HPV-related disease), followed by oral cavity (15.7 %) and nasopharynx (10.3 %). Twenty-five patients (12.2 %) received induction chemotherapy before CRT. Details on comorbidities, concomitant medications, and oncologic treatment are reported in Table 1. At the end of curative treatment, the median cumulative dose of CDDP was 250 mg/m^2 (200–300).

The clinical characteristics of patients developing CreaIncr vs. those who did not are detailed in Table 2.

Ninety patients (44 %) suffered from C-AKI, any grade occurred within the first cycle of CDDP; a grade I AKI was observed in approximately half of cases (51.1 %). Out of the 90 patients developing AKI, 76 (84.4 %) received high-dose CDDP, the remaining 14 subjects (15.6 %) a weekly schedule. Twenty-four patients (26.7 %) shifted to carboplatin during CRT.

Out of the 153 patients treated with high-dose cisplatin, data about fractionation were available in 94.1 % of cases (9 missing): 75 % (108 subjects) received a single-day cisplatin bolus, the remaining 25 % a fractionated scheme over two (34 patients) or three days (2 patients). The frequency of CreaIncr was 52.7 % (57/108) in patients receiving a one-day cisplatin bolus vs. 47.2 % (17/36) in those treated with fractionated cisplatin ($p = 0.57$).

On the univariable logistic regression model (Table 3), male sex (OR 3.20; 95 % CI 1.59–6.46; $p = 0.001$), higher BMI (25 vs 18: OR 8.24; 95 % CI 1.84–36.94; $p = 0.008$), larger BSA (1.99 vs 1.69: OR 3.04; 95 % CI 1.34–6.87; $p = 0.001$), older age (60 vs 40: OR 7.52; 95 % CI 2.28–24.87; $p = 0.004$), higher serum uric acid (5 vs 3: OR 4.80; 95 % CI 1.70–13.60; $p = 0.006$) and creatinine (OR 2.62; 95 % CI 1.68–4.09; $p < 0.001$) level, concomitant drugs (OR 1.48; 95 % CI 1.00–2.18; $p = 0.050$), and a high-dose cisplatin (one-day bolus vs. weekly: OR 2.95; 95 % CI 1.44–6.08; fractionated high-dose vs. weekly: OR 2.36; 95 % CI 0.96–5.8; $p = 0.015$).

were significantly associated with a higher rate of C-AKI. BMI, BSA, age, and serum acid uric was non-linearly associated with CreaIncr, with an initial increasing risk and a stabilization beyond the thresholds

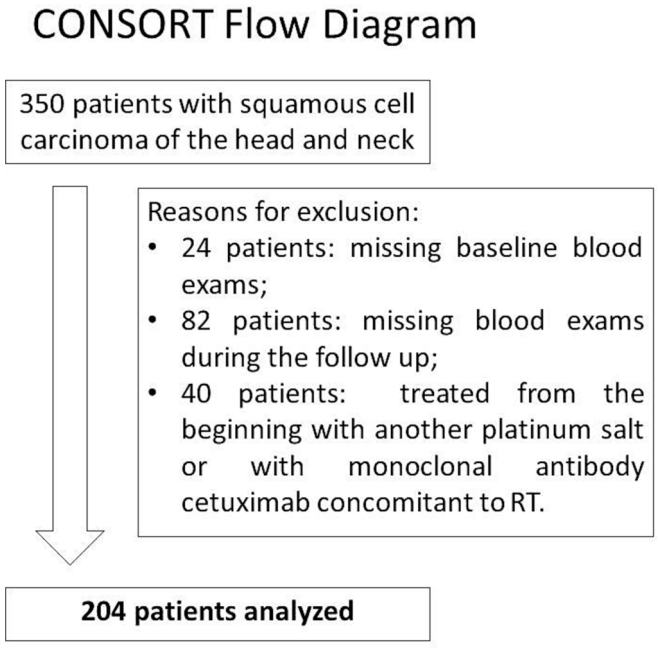

Fig. 1. CONSORT diagram.

Table 1
Baseline clinical characteristics of locally advanced-head and neck cancer patients.

	Overall
	N = 204 (%)
Sex	
Female	53 (26.0)
Male	151 (74.0)
Age (years)	
Median (1st and 3rd quartile)	56.0 (51.0; 63.0)
Tumor site	
Oropharynx	134 (65.7)
HPV +	99 (74)
HPV -	35 (26)
Oral cavity	32 (15.7)
Nasopharynx	21 (10.3)
Other (larynx-hypopharynx-paranasal sinus)	17 (8.3)
BMI (kg/m^2)	
Median (1st and 3rd quartile)	24.5 (22.0; 26.8)
BSA (m^2, Mosteller method)	
Median (1st and 3rd quartile)	1.85 (1.69; 1.99)
Comorbidities	
Diabetes	8 (3.9)
Hypertension	54 (26.5)
Hypercolesterolemia	19 (9.3)
Concomitant drugs	
Anti-hypertensive drugs	
Angiotensin-receptor blockers	24 (11.8)
Diuretics	18 (8.8)
Angiotensin converting enzyme-inhibitors	17 (8.3)
Calcium-blockers	11 (5.4)
Other	2 (1.3)
Statins	18 (8.8)
Other concomitant drugs (NSAIDs)	9 (4.4)
Curative treatment	
Definitive	152 (74.5)
Post-operative	52 (25.5)
Schedule of CDDP administration	
Weekly	51 (25.0)
Three-weekly One-day bolus	153 (75.0)
Fractionated over 2–3 days	108 (70.6)
Fractioning not specified	36 (23.5)
	9 (5.9)
CDDP total dose (mg/m2) at the end of the curative treatment	
Median (1st and 3rd quartile)	250 (200; 300)
Shift to other platinum salt during the treatment (%)	
No	173 (84.8)
Yes	31 (15.2)
Creatinine at baseline (mg/dL)	
Median (1st and 3rd quartile)	0.80 (0.67; 0.89)
Creatinine clearance at baseline (mL/min)	
Median (1st and 3rd quartile)	108.5 (98.0; 129.3)
Albumin at baseline (g/dL)	
Median (1st and 3rd quartile)	4.3 (4.1; 4.5)
Blood urea nitrogen at baseline (mg/dL)	
Median (1st and 3rd quartile)	31.0 (26.0; 39.0)
Serum uric acid at baseline (mg/dL)	
Median (1st and 3rd quartile)	4.90 (4.11; 5.74)
Magnesium at baseline (mg/dL)	
Median (1st and 3rd quartile)	1.99 (1.90; 2.11)

Table 2
Clinical characteristics of patients who developed AKI after the first cycle of CDDP.

	No CreaIncr N = 114 (%)	CreaIncr N = 90 (%)	SMD
AKI-KDIGO score			—
Stage I	—	46 (51.1)	
Stage II	—	39 (43.3)	
Stage III	—	5 (5.6)	
Sex			0.493
Female	40 (35.1)	13 (14.4)	
Male	74 (64.9)	77 (85.6)	
Age (years)			0.393
Median (1st and 3rd quartile)	54.5 (49.0; 62.0)	58.0 (52.0; 63.0)	
Tumor site			0.369
Oral cavity	23 (20.2)	9 (10.0)	
Oropharynx	70 (61.4)	64 (71.1)	
Nasopharynx	14 (12.3)	7 (7.8)	
Other (larynx-hypopharynx-paranasal sinus)	7 (6.1)	10 (11.1)	
Schedule of CDDP administration			0.404
Weekly	37 (32.5)	14 (15.6)	
Three-weekly	77 (67.5)	76 (84.4)	
One-day bolus	51 (44.7)	57 (63.3)	
Fractionated over 2–3 days	19 (16.7)	17 (18.9)	
Fractioning not specified	7 (6.1)	2 (2.2)	
Shift to other platinum salt during the treatment (%)			0.577
No	107 (93.9)	66 (73.3)	
Yes	7 (6.1)	24 (26.7)	
BMI (kg/m^2)			0.568
Median (1st and 3rd quartile)	23.3 (21.1; 26.3)	25.7 (23.4; 27.2)	
BSA (m^2, Mosteller method)			0.624
Median (1st and 3rd quartile)	1.79 (1.60; 1.91)	1.90 (1.80; 2.00)	
Diabetes			0.264
No	112 (98.2)	84 (93.3)	
Yes	2 (1.8)	6 (6.7)	
Hypertension			0.188
No	88 (77.2)	62 (68.9)	
Yes	26 (22.8)	28 (31.1)	
Anti-hypertensive drugs			0.298
Angiotensin converting enzyme-inhibitors	7 (6.1)	10 (11.1)	
Calcium-blockers	7 (6.1)	4 (4.4)	
Angiotensin-receptor blockers	10 (8.8)	14 (15.6)	
Diuretics			0.074
No	105 (92.1)	81 (90.0)	
Yes	9 (7.9)	9 (10.0)	
Loop-diuretics			0.268
No	112 (98.2)	83 (92.2)	
Yes	2 (1.8)	7 (7.8)	
Thiazide diuretics			0.054
No	109 (95.6)	85 (94.4)	
Yes	5 (4.4)	5 (5.6)	
Number of concomitant drugs			0.309
0	81 (71.1)	51 (56.7)	
1	23 (20.2)	27 (30.0)	
2	9 (7.9)	10 (11.1)	
3	1 (0.9)	2 (2.2)	
Hypercolesterolemia			0.110
No	105 (92.1)	80 (88.9)	
Yes	9 (7.9)	10 (11.1)	
Statins			0.074
No	105 (92.1)	81 (90.0)	
Yes	9 (7.9)	9 (10.0)	
Creatinine at baseline (mg/dL)			0.677
Median (1st and 3rd quartile)	0.73 (0.66; 0.84)	0.86 (0.79; 0.93)	
Creatinine clearance at baseline (mL/min)			0.010
Median (1st and 3rd quartile)	109.5 (98.0; 129.8)	105.0 (98.3; 127.0)	
Albumin at baseline (g/dL)			0.047
Median (1st and 3rd quartile)	4.3 (4.0; 4.5)	4.3 (4.1; 4.6)	
Blood urea nitrogen at baseline (mg/dL)			0.302
Median (1st and 3rd quartile)	30.0 (25.0; 36.0)	34.5 (27.0; 40.0)	
Serum uric acid at baseline (mg/dL)			0.411
Median (1st and 3rd quartile)	4.55 (3.87; 5.43)	5.20 (4.54; 6.05)	
Magnesium at baseline (mg/dL)			0.003
Median (1st and 3rd quartile)	2.00 (1.90; 2.10)	1.99 (1.90; 2.12)	

Abbreviation: SMD, standardized mean difference.

reported as the first comparison term. The administration of loop diuretics appeared as a potential risk factor (OR 4.74; 95 % CI 0.96–23.44; p = 0.162), even if it did not reach a statistical significant level.

On the multivariable model, age (60 vs. 40 years: OR 6.26; 95 % CI 1.34–29.21; p = 0.034), creatinine at baseline (0.89 vs 0.69: OR 2.39; 95 % CI 1.22–4.68; p = 0.027), number of concomitant drugs (≥1 vs. 0: OR 2.27; 95 % CI 1.03–5.03; p = 0.043), and schedule of CDDP administration (one-day bolus vs. weekly: OR 8.03; 95 % CI 2.84–22.68; fractionated high-dose vs. weekly: OR 4.22; 95 % CI 1.28–13.92; p = 0.001) maintained their significant association (Table 3).

Long-term renal outcome data were available for 202 patients (99 %). The frequency of grade ≥ 1 creatinine increase within 90 days from the conclusion of CRT was 81.1 % (73/90) in patients with an early CreaIncr vs. 58.9 % (66/112) in those without (p = 0.00076).

Discussion

Our monocentric retrospective analysis showed that 44 % of LA-HNSCC patients suffered from AKI according to KDIGO score [15]. Out of these patients, a severe (grade III) AKI was observed in a modest fraction of cases (5.6 %). The majority (84.4 %) of patients suffering from a C-AKI were on CRT with high-dose cisplatin (100 mg/m^2 every three weeks). Therefore, nephrotoxicity is confirmed to be a frequent complication of cisplatin-based CRT for LA-HNSCC, especially when CDDP is used at high doses.

C-AKI has been reported to occur in various percentages according to CDDP dose and also depending on the used renal toxicity score definition and grading. For example, in a specific cohort of HNSCC patients, CDDP-induced nephrotoxicity ranged from 1 % to 69 % [7,18–20], with the highest percentage among the highest dosage of CDDP (100 mg/m^2 every three weeks). Harmonization in terms of AKI definitions across studies are essential to draw conclusions. In this context, standardizing the definition of AKI provides a clear framework for clinicians to avoid ungraded statements; AKI defined with KDIGO score allows the identification of low-stage AKI. KDIGO builds upon two earlier AKI classification systems: the Acute Kidney Injury Network (AKIN) and the Risk, Injury, Failure, Loss, End-Stage (RIFLE) criteria. Compared to AKIN and RIFLE, the incidence of AKI according to KDIGO is the highest one due to the addition of an absolute increase criterion (≥0.3 mg/dl over 48 h) to the RIFLE definition and expansion of the time limit for percentage increase (≥50 %) in the AKIN definition from 48 h to 7 days [21]. Therefore, AKI will be more frequently diagnosed at an early stage if KDIGO is applied, as seen in our series. AKI definitions based on the most used international systems (KDIGO and CTCAE) are provided in Table 4.

In definitions and classifications, the grading system has evolved. Indeed, while version 4.0 of the CTCAE (used in this article) considered five grades of AKI, the newer one (version 5.0 published in 2017) had significant modifications (Table 5): grades 1 and 2 were removed, G3 was defined as the need of hospitalization, while grade 4 and 5 remained unchanged. Such a new definition of the AKI is independent of the creatinine level. It helps simplify grading the adverse event while not creating potentially misleading descriptions that may overlap with other adverse events. The heterogeneity of renal damage assessment timings is

Table 3
Results of univariable logistic model and multivariable model for AKI after the first course of CDDP.

	Univariable models			Multivariable model		
	OR	95 % CI	p	OR	95 % CI	p
Sex			0.001			0.335
Male vs Female	3.20	(1.59; 6.46)		0.55	(0.16–1.86)	
Hypertension			0.183			0.254
Yes vs No	1.53	(0.82; 2.86)		0.51	(0.16–1.63)	
Diabetes			0.095			0.372
Yes vs No	4.00	(0.79; 20.32)		2.57	(0.32–20.39)	
BMI* (kg/m^2)			0.008			0.877
25 vs 18	8.24	(1.84; 36.94)		1.74	(0.18–16.57)	
30 vs 25	1.47	(0.60; 3.56)		1.07	(0.41–2.78)	
BSA* (m^2, Mosteller method)			0.001			0.775
1.99 vs 1.69**	3.04	(1.34; 6.87)		1.48	(0.50–4.34)	
Age* (years)			0.004			0.034
60 vs 40	7.52	(2.28; 24.87)		6.26	(1.34–29.21)	
70 vs 60	0.59	(0.31; 1.14)		0.48	(0.20–1.19)	
Serum uric acid* (mg/dL)			0.006			0.235
5 vs 3	4.80	(1.70; 13.60)		3.10	(0.79–12.23)	
7 vs 5	1.03	(0.47; 2.29)		0.61	(0.21–1.76)	
Magnesium at baseline* (mg/dL)			0.688			0.576
2.11 vs 1.90**	1.02	(0.70; 1.48)		0.98	(0.57–1.71)	
Albumin at baseline* (g/dL)			0.855			0.238
4.5 vs 4.1**	0.93	(0.68; 1.28)		0.71	(0.45–1.12)	
Creatinine at baseline* (mg/dL)			<0.001			0.027
0.89 vs 0.69**	2.62	(1.68; 4.09)		2.39	(1.22–4.68)	
Creatinine clearance at baseline* (mL/min)			0.771			0.350
129.2 vs 98.0**	1.10	(0.74; 1.62)		1.48	(0.86–2.55)	
Blood urea nitrogen at baseline* (mg/dL)			0.099			—
39 vs 26**	1.47	(1.01; 2.15)		—	—	
Diuretics			0.162			—
Loop diuretics vs No	4.74	(0.96; 23.44)		—	—	
Tiaz vs No	1.08	(0.28; 4.17)		—	—	
Number of concomitant drugs			0.050			0.043
1 vs 0	1.48	(1.00; 2.18)		2.27	(1.03–5.03)	
Induction chemotherapy before CRT			0.089			0.216
Yes vs no	0.45	(0.18–1.13)		0.45	(0.13–1.59)	
Schedule of CDDP administration			0.015			0.001
One-day bolus vs Weekly	2.95	(1.44–6.08)		8.03	(2.84–22.68)	
Fractionated over 2–3 days vs Weekly	2.36	(0.96–5.80)		4.22	(1.28–13.92)	
Fractioning not specified vs Weekly	0.76	(0.14–4.08)		1.71	(0.19–15.44)	

Abbreviations: OR, odds ratio; CI: confidence interval; p, two-sided Wald test p value.
*Modelled as restricted cubic spline.
**Values represent third and first quartile of the variable distribution.

Table 4
Differences of AKI definitions based on the classification system.

KDIGO	CTCAE v4.0	CTCAE v5.0
Any of the following: Increase in serum creatinine by $\geq$ 0.3 mg/dl within 48 h Increase in serum creatinine to $\geq$ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days Urine volume < 0.5 ml/kg/h for 6 h.	A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and postrenal causes (ureteral or bladder outflow obstruction).	A disorder characterized by the acute loss of renal function (within 2 weeks) and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).

an additional factor that makes it more difficult to compare the findings published in the literature. In our study, the 90-day cutoff was chosen to maximize the possibility of deeming the persistent nephrotoxicity cisplatin-related, minimizing potential confounders. A creatinine increase found after more than three months from the last administration of CRT is unlikely to be interpreted as directly cisplatin-related. Indeed, it might be due to subsequent medications or concomitant medical disorders, which may have influenced the occurrence of a late renal dysfunction.

Although no direct comparisons can be made between clinical studies, some similarities and differences may be appreciated between the present retrospective study and the JCOG1008 trial [10,11], a randomized phase II/III study showing a non-inferiority of concurrent CRT with weekly cisplatin (40 mg/m^2) compared with concurrent CRT with 3-weekly cisplatin (100 mg/m^2) for post-operative high-risk patients with LA-HNSCC [10]. AKI was observed in 31.1 % of patients treated with a weekly schedule versus 43.4 % with a three-weekly schedule [11]. Thus, patients at higher risk of developing C-AKI could be safely offered a weekly schedule. However, although in the JCOG1008 trial no detriment in survival was observed in patients receiving lower doses of cisplatin [11], patients in the weekly schedule arm received a lower cumulative CDDP dose than those randomized to high-dose chemotherapy (weekly 239 mg/m^2 vs. three-weekly 280 mg/m^2). In our series, the cumulative dose of cisplatin was 250 mg/m^2 (IQR 200–300); no differences in the total cumulative dose were observed between the weekly and three-weekly schedules. The median total cumulative dose of cisplatin among those patients who experienced creatinine increase was 200 mg/m^2 [10,11]. Although the definition of renal damage was consistent in the two studies (based on KDIGO in both cases), its time correlate differed between them. The percentages reported in the randomized trial referred to any nephrotoxicity occurring in the first 30 days after CRT. On the contrary, we aimed at identifying and tackling an early kidney damage, so we considered any C-AKI occurring in the first 6–20 days of CRT. With these differences, the frequency of C-AKI in our patients seemed to be higher than what observed in the prospective trial.

Table 5
CTCAE grading systems to classify the severity of the main adverse events describing kidney damage.

AE	CTCAE	G1	G2	G3	G4	G5
Acute kidney injury	v4.0	Creatinine level increase of > 0.3 mg/dL; creatinine 1.5—2.0 × above baseline	Creatinine 2—3 × above baseline	Creatinine > 3 × baseline or > 4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
	v5.0	Removed	Removed	Hospitalization indicated	Unchanged	Unchanged
Chronic kidney disease	v4.0 and v5.0	eGFR or CrCl < LLN − 60 ml/min/1.73 m2 or proteinuria 2 + present; urine protein/creatinine > 0.5	eGFR or CrCl 59 – 30 ml/min/1.73 m2	eGFR or CrCl 29 – 15 ml/min/1.73 m2	eGFR or CrCl < 15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Creatinine increased	v4.0	>1—1.5 × baseline; >ULN − 1.5 × ULN	>1.5—3.0 × baseline; >1.5—3.0 × ULN	>3.0 baseline; >3.0—6.0 × ULN	>6.0 × ULN	–
	v5.0	>ULN − 1.5 × ULN (removed ">1—1.5 × baseline")	Unchanged	Unchanged	Unchanged	–

*underlined the update of the previous version.
Abbreviations: AE, Adverse Event; AKI, Acute Kidney Injury; CTCAE, Common Terminology Criteria for Adverse Events; CrCl, creatinine clearance; eGFR, Estimated Glomerular Filtration Rate; G, Grade; LLN, Lower Limit of Normal; ULN, Upper Limit of Normal; v, Version.

However, it is worth noting that the JCOG1008 study protocol foresaw lab test assessments on a weekly basis [10], while in our clinical practice we perform further tests 24–48 h after each administration of high-dose CDDP, while for weekly cisplatin they are performed on a case-by-case basis (e.g., earlier assessment of lab test in subjects suffering from nausea to intercept a potential dehydration that may hamper the feasibility of further cycles of cisplatin). This different timing and the higher percentage of subjects receiving a three-weekly schedule (75 % in our retrospective series) may explain the differences observed in the two studies.

In terms of preventing CDDP-related nephrotoxicity, one of the standard approaches is to guarantee intravenous hydration, even if the optimal schedule of hydration is not yet clarified. Also, providing magnesium supplementation (due to specific CDDP toxicity) in conjunction with hydration is routinely used in clinical practice, but still controversial [13,22]. In our analysis, baseline serum magnesium was not significantly related to CreaIncr.

Literature data suggest that mannitol forced diuresis may be considered to prevent C-AKI, whereas furosemide is neither suggested as a nephroprotective agent nor is it regarded as a potential nephrotoxic drug [13]. In our clinical routine, patients do not receive diuretics after chemotherapy. However, mannitol or loop diuretics may be administered on a case by case basis if post-treatment fluid retention occurs. In this context, we observed that patients on chronic loop diuretics had a non-significant higher risk of developing CreaIncr during treatment.

Insufficient oral hydration and food intake due to chemotherapy- or radiotherapy-induced nausea and vomiting, pain, and dysphagia could increase the risk of C-AKI. High peak plasma-free platinum concentration has been correlated with nephrotoxicity. Moreover, glomerular filtration rate and plasma magnesium concentrations decreased after cisplatin doses higher than 50 mg/m^2 BSA, but rarely changed if the dose was below 20 mg/m^2. Moreover, glomerular filtration rate and plasma magnesium concentrations decreased after cisplatin doses higher than 50 mg/m^2 BSA in a dose-dependent manner as they decrease with increasing doses [23–25].

Although the frequency of CreaIncr in patients receiving a one-day cisplatin bolus was slightly higher (5 %) than in subjects receiving a drug fractionation over two or three days, this modest difference was not statistically significant (p = 0.57) in our study. Similarly, the recent CisFRad trial has shown that renal impairment among those patients treated with a fractionated schedule (25 mg/m^2 per day/d1^{-4}(−|-), once every three weeks for 3 cycles) was not significantly different to the one observed in patients treated with a single high-dose administration [26]. Therefore, with the caveat of the retrospective nature of our observation, in patients eligible for high-dose cisplatin, the drug fractionation over two or three days did not significantly reduce the risk of early kidney injury during CRT over a single-day bolus.

The development of a risk prediction model in LA-HNSCC patients is based on the identification of pre-treatment factors for better patient selection before starting CRT. In this scenario, Motwani SS et al. [27] published a risk prediction model to identify risk factors for cisplatin-acute kidney injury (C-AKI) after the first course; the data were collected on more than 4,400 patients with various cancers (including head and neck) treated with cisplatin, and C-AKI occurred in approximately 13 % of patients. Predictive factors for C-AKI included age, arterial hypertension, cisplatin dose, and hypoalbuminemia. A score-based model was proposed using these parameters. One of the limitations of this study is that it included any cancer type, not only HNSCC. Patients were unselected for disease stage (cisplatin could be delivered either in the curative setting for locally or regionally advanced disease or as an adjuvant treatment with other chemotherapy drugs or in the palliative setting as a component of treatments for advanced/metastatic disease). Moreover, the model was not specific for subjects receiving cisplatin concomitantly with radiotherapy.

Our study suggests that BMI or BSA, age, baseline serum creatinine and uric acid, and potentially nephrotoxic drugs (such as NSAIDs) could be good predictors of C-AKI in HNSCC patients treated with CDDP-based CRT, and should be evaluated at baseline.

Literature data showed that older age and female sex were reported to be risk factors [18]. In our multivariable analysis, older age was significantly related to the risk of CDDP nephrotoxicity, while sex did not. This was in contrast to some previous studies that revealed a higher sensitivity against CDDP-induced nephrotoxicity for women [28–30]. Indeed, in our study, men had a significant association with higher rate of C-AKI on the univariable logistic regression model.

Our study did not support hypoalbuminemia as a potential risk factor for nephrotoxicity as others [27], likely due to a narrower patient selection through the identification of higher risk patients based on low baseline levels of albumin (2.0 to 3.5 g/dl).

In our series baseline creatinine clearance was not related to C-AKI. This might be explained by the positive selection of our cases. Indeed, although we considered platinum-eligible subjects with eGFR ≥ 60 ml/min, the baseline creatinine clearance observed in our study population was much higher (median 108.5 ml/min, IQR 98–129.3). Therefore, we may posit that eGFR is a good selector for discriminating cisplatin-eligible from ineligible patients, but not a predictive factor for C-AKI in subjects already deemed fit for cisplatin. In this scenario, at multivariable analysis, higher baseline creatinine was associated with a higher risk of C-AKI. Nevertheless, a study showed how AKI stage II in HNSCC patients is underestimated and is one of the major factors for discontinuing CDDP during curative CRT [20]. In our cases, 26.7 % of patients with CreaIncr discontinued CDDP and shifted to carboplatin.

The frequency of any grade late creatinine increase was significantly higher in patients experiencing a C-AKI compared to those without (absolute difference of 22.2 %, p = 0.00076). This observation suggests that early cisplatin-related kidney damage implies a late renal

dysfunction. On one side, supportive interventions administered after CreaIncr could not revert the early cisplatin-related kidney injury to normal renal functionality. At the same time, given the early timing of the CreaIncr assessment (i.e., within 20 days from CRT start), we hypothesize that the timely detection of C-AKI has reduced the probability of subsequent further renal damage, possibly with higher-grade adverse events, thanks to the supportive treatments aimed at limiting nephrotoxicity during CRT. Indeed, the prevalence of G3 CreaIncr in the first three months after the conclusion of CRT was modest (<1%, 2/202; both patients had a G3 C-AKI after a one-day bolus of high-dose cisplatin). On the contrary, in most subjects with persistent nephrotoxicity, the renal dysfunction was not severe (G1 in 118/139 cases, 84.8 %). Besides, early detection of C-AKI would enable administering alternative therapeutic regimens (e.g., switch from CDDP to carboplatin) to maximize the opportunity to deliver systemic treatments concurrently with curative or adjuvant radiation in due time.

The low number of patients and the absence of a validation cohort impaired us in the development of a predictive nomogram, and hampered the feasibility of refined analyses to predict the severity of C-AKI (i.e., only 5.6 % of cases had a grade III AKI). Other limitations of the study are its retrospective nature, and the inclusion of patients treated with both definitive and post-operative CRT, which are known to be associated with a different radiation dose, and potentially different toxicities, notably dysphagia or nausea. Furthermore, the small number of events (24/204, 11.76 %) limited the feasibility of survival analyses in our population (both median follow-up and overall survival were not reached, data not shown).

Another drawback of this study is that the patient population received different schedules of cisplatin administration, and 12 % were treated with induction chemotherapy before CRT. Nevertheless, neoadjuvant treatment had no impact on the risk of subsequent C-AKI (not statistically significant at both univariate and multivariable analyses). Moreover, despite the absence of significant differences in CreaIncr in patients receiving a one-day bolus vs. fractionated high-dose cisplatin, we included the CDDP fractionation in the multivariable analysis, and we did not observe any significant difference between the two schedules. At the same time, we confirmed the lower risk of C-AKI in patients receiving weekly cisplatin compared to those treated with high-dose chemotherapy independently of the fractionation (one-day bolus vs. fractionated over two or three days). These considerations mitigate the substantial heterogeneity potentially affecting the results in this retrospective analysis.

Furthermore, in our study, we focused on events of C-AKI that occurred within the first cycle of CDDP and this has potentially underestimated the incidence of C-AKI, missing the events that occurred in subsequent courses. However, our findings may help select patients who could be treated by cisplatin-based CRT with a limited risk of early C-AKI.

As future perspectives, recent data have shown that the use of avasopasem manganese, an investigational agent assessed for the control of radiation-induced mucositis in LA-HNSCC patients, is safe and active in protecting from cisplatin-related chronic kidney damage [31]. Although nephroprotective drugs may reduce long-term kidney injury, there is still a strong need to limit the acute one. In this context, strict monitoring of AKI, defined and staged according to KDIGO, graded according to the latest version of the CTCAE, and assessed early during the first weeks of CRT, since the very beginning of cisplatin-based treatment is strongly recommended to avoid dose adjustments, interruptions, and delays that might result from various toxicities. The risk factors evaluated in our study could be easily available as baseline clinical data to improve decision-making in a setting where CDDP has a curative significance.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Adelstein DJ, Li Y, Adams GL, Wagner H, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. Journal of Clinical Oncology 2003;21:92–8. https://doi.org/10.1200/JCO.2003.01.008.

[2] Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer. 101056/NEJMoa031317 2003;349:2091–8. 10.1056/NEJMOA031317.

[3] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner RH, et al. Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer. 101056/NEJMoa032641 2004;350:1945–52. 10.1056/NEJMOA032641.

[4] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck. 101056/NEJMoa032646 2004;350:1937–44. 10.1056/NEJMOA032646.

[5] Strojan P, Vermorken JB, Beitler JJ, Saba NF, Haigentz M, Bossi P, et al. Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: A systematic review. Head & Neck 2016;38:E2151–8. https://doi.org/10.1002/HED.24026.

[6] Szturz P, Wouters K, Kiyota N, Tahara M, Prabhash K, Noronha V, et al. Weekly low-dose versus three-weekly high-dose cisplatin for concurrent chemoradiation in locoregionally advanced non-nasopharyngeal head and neck cancer: A systematic review and meta-analysis of aggregate data. The Oncologist 2017;22:1056–66. https://doi.org/10.1634/THEONCOLOGIST.2017-0015.

[7] Van Der Vorst MJDL, Neefjes ECW, Toffoli EC, Oosterling-Jansen JEW, Vergeer MR, Leemans CR, et al. Incidence and risk factors for acute kidney injury in head and neck cancer patients treated with concurrent chemoradiation with high-dose cisplatin. BMC Cancer 2019;19:1–10. https://doi.org/10.1186/S12885-019-6233-9/FIGURES/3.

[8] Panihar C, Rawat S, Singotia L, Raj A, Jain RK. A prospective randomised comparative study between weekly cisplatin versus three weekly cisplatin with radiotherapy in unresectable locally advanced head and neck cancer. Indian J Otolaryngol Head Neck Surg 2022;74:2670–5. https://doi.org/10.1007/S12070-020-02350-6.

[9] An open-label, noninferiority phase III RCT of weekly versus three weekly cisplatin and radical radiotherapy in locally advanced head and neck squamous cell carcinoma (ConCERT trial). | Journal of Clinical Oncology n.d. https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.6004 (accessed April 5, 2023).

[10] Kiyota N, Tahara M, Mizusawa J, Kodaira T, Fujii H, Yamazaki T, et al. Weekly Cisplatin Plus Radiation for Postoperative Head and Neck Cancer (JCOG1008): A Multicenter, Noninferiority, Phase II/III Randomized Controlled Trial. Journal of Clinical Oncology 2022;40:1980–90. https://doi.org/10.1200/JCO.21.01293.

[11] Kiyota N, Tahara M, Kodaira T, Hayashi R, Nishino H, Asada Y, et al. Impact of acute kidney injury on overall survival in postoperative patients with head and neck cancer who received chemoradiotherapy with cisplatin: A supplementary analysis of a phase II/III trial of JCOG1008. 101200/JCO20234116_suppl6079 2023;41:6079–6079. 10.1200/JCO.2023.41.16_SUPPL.6079.

[12] Cvitkovic E, Spaulding J, Bethune V, Martin J, Whitmore WF. Improvement of cis-dichlorodiammineplatinum (NSC 119875): Therapeutic index in an animal model. Cancer 1977;39:1357–61. https://doi.org/10.1002/1097-0142.

[13] Crona DJ, Faso A, Nishijima TF, McGraw KA, Galsky MD, Milowsky MI. A Systematic Review of Strategies to Prevent Cisplatin-Induced Nephrotoxicity. The Oncologist 2017;22:609–19. https://doi.org/10.1634/THEONCOLOGIST.2016-0319.

[14] Tao Y, Aupérin A, Sun X, Sire C, Martin L, Coutte A, et al. Avelumab–cetuximab–radiotherapy versus standards of care in locally advanced squamous-cell carcinoma of the head and neck: The safety phase of a randomised phase III trial GORTEC 2017–01 (REACH). European Journal of Cancer 2020;141:21–9. https://doi.org/10.1016/J.EJCA.2020.09.008.

[15] Khwaja A. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Nephron. Clinical Practice 2012;120:c179–84. https://doi.org/10.1159/000339789.

[16] Flury BK, Riedwyl H. Standard distance in univariate and multivariate analysis. The American Statistician 1986;40:249–51. https://doi.org/10.1080/00031305.1986.10475403.
[17] Durrleman S, Simon R. Flexible regression models with cubic splines. Statistics in Medicine 1989;8:551–61. https://doi.org/10.1002/sim.4780080504.
[18] Faig J, Haughton M, Taylor RC, D'Agostino RB, Whelen MJ, Porosnicu Rodriguez KA, et al. Retrospective Analysis of Cisplatin Nephrotoxicity in Patients With Head and Neck Cancer Receiving Outpatient Treatment With Concurrent High-dose Cisplatin and Radiotherapy. American Journal of Clinical Oncology 2018;41:432–40. https://doi.org/10.1097/COC.0000000000000301.
[19] Fan KY, Gogineni H, Zaboli D, Lake S, Zahurak ML, Best SR, et al. Comparison of acute toxicities in two primary chemoradiation regimens in the treatment of advanced head and neck squamous cell carcinoma. Annals of Surgical Oncology 2012;19:1980–7. https://doi.org/10.1245/S10434-012-2219-4/TABLES/5.
[20] Hoek J, Bloemendal KM, van der Velden LAA, van Diessen JNA, van Werkhoven E, Klop WMC, et al. Nephrotoxicity as a Dose-Limiting Factor in a High-Dose Cisplatin-Based Chemoradiotherapy Regimen for Head and Neck Carcinomas. Cancers 2016, Vol 8, Page 21 2016;8:21. 10.3390/CANCERS8020021.
[21] Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. Clinical Journal of the American Society of Nephrology 2014;9:12–20. https://doi.org/10.2215/CJN.02730313/-/DCSUPPLEMENTAL.
[22] Yoshida T, Niho S, Toda M, Goto K, Yoh K, Umemura S, et al. Protective Effect of Magnesium Preloading on Cisplatin-induced Nephrotoxicity: A Retrospective Study. Japanese Journal of Clinical Oncology 2014;44:346–54. https://doi.org/10.1093/JJCO/HYU004.
[23] Cornelison TL, Reed E. Nephrotoxicity and Hydration Management for Cisplatin, Carboplatin, and Ormaplatin. Gynecologic Oncology 1993;50:147–58. https://doi.org/10.1006/GYNO.1993.1184.
[24] Hodgkinson E, Neville-Webbe HL, Coleman RE. Magnesium Depletion in Patients Receiving Cisplatin-based Chemotherapy. Clinical Oncology 2006;18:710–8. https://doi.org/10.1016/J.CLON.2006.06.011.
[25] Ozkok A, Edelstein CL. Pathophysiology of cisplatin-induced acute kidney injury. Biomed Research International 2014. https://doi.org/10.1155/2014/967826.
[26] Borel C, Sun X, Coutte A, Bera G, Zanetta S, Alfonsi M, et al. 914MO Standard versus fractionated high dose cisplatin concomitant with radiotherapy in locally advanced head & neck squamous cell cancer (LA-HNSCC): Results of the GORTEC 2015–02 CisFRad randomized trial. Annals of Oncology 2020;31:S660. https://doi.org/10.1016/j.annonc.2020.08.1029.
[27] Motwani SS, McMahon GM, Humphreys BD, Partridge AH, Waikar SS, Curhan GC. Development and Validation of a Risk Prediction Model for Acute Kidney Injury After the First Course of Cisplatin. Journal of Clinical Oncology 2018;36:682–8. https://doi.org/10.1200/JCO.2017.75.7161.
[28] De Jongh FE, Van Veen RN, Veltman SJ, De Wit R, Van Der Burg MEL, Van Den Bent MJ, et al. Weekly high-dose cisplatin is a feasible treatment option: analysis on prognostic factors for toxicity in 400 patients. British Journal of Cancer 2003;88(888):1199–206. https://doi.org/10.1038/sj.bjc.6600884.
[29] Chen WY, Hsiao CH, Chen YC, Ho CH, Wang JJ, Hsing CH, et al. Cisplatin Nephrotoxicity Might Have a Sex Difference. An analysis Based on Women's Sex Hormone Changes. Journal of Cancer 2017;8:3939–44. https://doi.org/10.7150/JCA.20083.
[30] Eshraghi-Jazi F, Nematbakhsh M. Sex Difference in Cisplatin-Induced Nephrotoxicity: Laboratory and Clinical Findings. J Toxicol 2022. https://doi.org/10.1155/2022/3507721.
[31] Mapuskar KA, Vasquez Martinez G, Pulliam CF, Petronek MS, Steinbach EJ, Monga V, et al. Avasopasem manganese (GC4419) protects against cisplatin-induced chronic kidney disease: An exploratory analysis of renal metrics from a randomized phase 2b clinical trial in head and neck cancer patients. Redox Biology 2023;60:102599. https://doi.org/10.1016/J.REDOX.2022.102599.