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Assessment of Renal Function in Head and Neck Cancer Patients Treated with Cisplatin: Different Biomarkers and Acute Kidney Injury Classifications

Nadine de Godoy Torso [1], Marília Berlofa Visacri [2], Julia Coelho França Quintanilha [1], Maria Aparecida Cursino [1], Eder de Carvalho Pincinato [1] and Patricia Moriel [3,*]

[1] School of Medical Sciences, University of Campinas, Campinas 13083-894, Brazil
[2] Faculty of Pharmaceutical Sciences, University of São Paulo, São Paulo 05508-000, Brazil
[3] Faculty of Pharmaceutical Sciences, University of Campinas, Campinas 13083-970, Brazil
* Correspondence: patricia.moriel@fcf.unicamp.br; Tel.: +55-19-35218153

Abstract: Cisplatin is associated with dose-limiting nephrotoxicity, and the timely detection of acute kidney injury (AKI) can affect morbimortality. Therefore, this study aimed to investigate the tools for monitoring renal function in AKI. This was a retrospective, cohort study. Cisplatin-treated patients with head and neck cancer were included. Nephrotoxicity was assessed using serum creatinine, estimated creatinine clearance, serum electrolytic alterations, and plasma kidney injury molecule-1 (KIM-1). The toxicity severity was classified according to Common Terminology Criteria for Adverse Events (CTCAE), and AKI was classified by Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) and Acute Kidney Injury Network (AKIN). A total of 81 participants were included, of whom only 32 did not have AKI. Almost 90% of participants had a decreased estimated glomerular filtration rate five (D5) days after chemotherapy. The AKI estimate differs between AKIN and RIFLE; more participants were diagnosed by the RIFLE at D5, 19.5% versus 2.4% by AKIN, and fifteen had a discordance between these classifications. All laboratory markers showed significant changes on D5. KIM-1 appeared a possible biomarker when considering CTCAE or AKIN classifications ($p < 0.05$ on D5), but not when RIFLE classification was used ($p = 0.0780$). Further studies may seek to understand the profiles of different biomarkers together.

Keywords: cisplatin; drug-related side effects and adverse reactions; acute kidney injury

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1. Introduction

Almost 800,000 new cases of head and neck squamous cell carcinoma (SCC) are reported annually [1]. Locally advanced disease (stages III and IV) represents the majority of cases, with current treatment strategies for these patients consisting of high-dose cisplatin concomitant with radiotherapy [2,3]. Despite its efficacy, cisplatin treatment is often associated with severe adverse effects, mainly as a consequence of its cytotoxic effects on healthy tissue cells. Nephrotoxicity is of particular significance; even with the accompanied use of diuretics and pre-hydration [4,5], nephrotoxicity is still a dose-limiting adverse effect [6]. Moreover, nephrotoxicity leads to a progressive decline in renal function in approximately 20–30% of patients [7]. Along with electrolyte disturbances and reduced renal filtration capacity [5], acute kidney injury (AKI) [8] is one of the main clinical manifestations of cisplatin-induced nephrotoxicity.

Thus, owing to its high prevalence and impact on treatment follow-up, it is essential to recognize nephrotoxicity for early intervention. There are currently three proposals for defining and classifying the severity of AKI: the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) [9] and the Acute Kidney Injury Network (AKIN) [10]; both consider changes in serum creatinine or urinary output and the estimated glomerular filtration rate

are presented. Nephrotoxicity markers were compared at baseline, D5, and D20 using Friedman's test. The Wilcoxon test was used to compare KIM-1 levels at baseline and D5. Data normality was tested using the Shapiro–Wilk test. The significance level adopted for all analyses was set at 5% ($p < 0.05$). All statistical analyses were performed using GraphPad Prism v.9.1.0 software. for Windows (GraphPad Software, Inc., San Diego, CA, USA).

5. Conclusions

The high incidence of patients with cisplatin nephrotoxicity reinforces the need for a more complete renal evaluation of these patients before, during, and after therapy. More participants were diagnosed with AKI according to the RIFLE consensus. KIM-1 was identified as a possible biomarker of kidney damage in patients treated with cisplatin when comparing its expression between participants who did not have any degree of nephrotoxicity and those who had, according to the CTCAE or AKIN, but not when RIFLE was adopted. It is still necessary to understand the profiles of different biomarkers together instead of just one or two isolated candidates.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Campinas (protocol code: 65397517.7.0000.5404, 8 February 2021).

Informed Consent Statement: Informed consent was obtained from all the subjects involved in the study.

Data Availability Statement: The datasets generated and/or analyzed during the current study are available from the Research Data Repository of the University of Campinas, https://redu.unicamp.br/dataset.xhtml?persistentId=doi:10.25824/redu/XT1BEY.

Conflicts of Interest: The J.C.F.Q. is an employee of Foundation Medicine, a wholly owned subsidiary of Roche, and has an equity interest in Roche. This work was conceived when J.C.F.Q. was a PhD student at the University of Campinas and does not represent a potential conflict of interest.