 

ORIGINAL ARTICLE

# Frequency of cisplatin-induced severe renal injury in patients with solid tumours on renal scintigraphy

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## Abstract

*Objective* Cisplatin is an effective chemotherapeutic drug for the treatment of solid tumours. However, its nephrotoxic side effects limit its optimal use and renal scintigraphy may be a reliable diagnostic tool for detecting, evaluating, and quantifying any cisplatin-induced nephrotoxicity. This cross-sectional retrospective study was designed to determine the frequency of cisplatin-induced severe renal injury by radionuclide renal scintigraphy in patients with solid tumours undergoing chemotherapy with cisplatin-based regimens. The at thuclear Medical Centre, Armed Forces Institute of Pathology (AFIP), .

*Methods* 62 patients (48 male, 14 female) who were candidates for cisplatin-based chemotherapy and had normal renal function as evidenced by normal serum urea and creatinine levels and a normal value of age-adjusted GFR on $^{99m}$Tc-99m-DTPA renal scintigraphy as per guidelines of National kidney Foundation, were subjected to post chemotherapy $^{99m}$Tc-DTPA renal scintigraphy within 02 weeks of completion of 06 cycles cisplatin-based chemotherapy.

*Results* The frequency of severe renal injury was calculated as 2/62 (3.2%) as determined by $^{99m}$Tc-DTPA scintigraphy after completion of 6 cycles of chemotherapy

*Conclusion* 3.2% of all patients developed severe renal injury at the completion of 6 cycles of cisplatin based chemotherapeutic regimen. This included patients with severe renal injury (GFR 15-29 ml/min) as well as patients with severe renal injury leading to absolute renal failure (GFR <15 ml/min).

***Key words**: $^{99m}$Tc-DTPA, bladder cancer cisplatin, renal injury, renal scintigraphy, solid tumours*

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## Introduction

Malignant neoplasms are found to be the second most important cause of death after cardiovascular mortality in demographic studies [1]. Prostrate, breast, lung, colon & rectum, skin and bladder cancers were the most common cancers respectively in US population in 2011. The three most common cancers among males are prostate (43%),

colorectal (9%) and melanoma of the skin(7%), and those among females are breast (41%), uterine corpus (8%), and colorectal (8%) [2].

Cisplatin is an effective chemotherapeutic anticancer drug for the treatment of solid tumours. However, its nephrotoxic side effects including early and delayed renal dysfunction are major concerns limiting its use [3, 4, 14].

Biochemical tests for evaluation of renal sufficiency including serum levels of urea, creatinine and creatinine clearance, have traditionally been used to measure baseline and post-therapy renal function in cancer patients undergoing chemotherapy regimens containing cisplatin [5]. However, renal scintigraphy is found to provide a more sensitive means for detecting, evaluating, and quantifying any renal insufficiency by calculating the glomerular filtration rate (GFR) [6]. By determining the GFR, renal impairment can be estimated and classified as mild, moderate, severe and renal failure as per the guidelines of National Kidney Foundation [7, 8]. The renal injury can be quantified by renal scintigraphy at an earlier stage before any significant derangement of renal function tests [7].

## Materials & Methods

This cross sectional observational study was conducted at the Nuclear Medical Centre, Armed Forces Institute of Pathology, Rawalpindi, from Dec 2012 to Dec 2013. Patients were referred from the Oncology department, Combined Military Hospital Rawalpindi. Informed written consent was obtained from patients and the study was approved by the Hospital Ethics Committee. Sampling technique was non-probability, consecutive.

Patients suffering from head and neck/lung, gynaecologica/lgastrointestinal/urinary bladder cancers, germ cell tumours and osteosarcomas, who were candidates for cisplatin-based chemotherapy regimen in higher dose 60-75 mg/m$^2$/03 weekly, non-hypertensive/non-diabetic with normal renal function (urea, creatinine), normal value of age-adjusted GFR on Tc-99m-DTPA renal scintigraphy as per guidelines of National Kidney Foundation [8] and no history of pre-existing renal disease were included in the study. Patients taking other nephrotoxic drugs or low-dose of cisplatin at <60 mg/m$^2$/3 weekly, known cases of renal failure or GFR less than normal value of age-adjusted GFR on Tc-99m-DTPA renal scintigraphy as per guidelines of National Kidney Foundation, hypertensive, diabetics, or haemodynamically unstable patients or those with a known history of known renal disease were excluded.

Necessary lab investigations were carried out at Armed Forces Institute of Pathology (AFIP), Rawalpindi while DTPA renal scintigraphy was carried out at the Nuclear Medical Centre, AFIP, Rawalpindi. Serum urea and creatinine levels were determined by an automated analyzer to identify patients with normal renal function.

A post chemotherapy Tc-99m-DTPA renal scan was conducted within 02 weeks of completion of 6 cycles of cisplatin-based chemotherapy. For Tc-99m-DTPA renal scintigraphy, 555 MBq dose of Tc-99m-DTPA was administered intravenously. Blood flow study of 30 frames in first 30-sec (1 frame per sec) followed by dynamic study of 60 frames in 30 min (1 frame per 30-sec) was obtained using a large field-of-view ECAM gamma camera with a low-energy all-purpose parallel hole collimator. Photopeak was centered at 140 keV with 20% window. The regions-of-interest for the kidneys and their background were drawn and time-activity curves for the 30-sec flow phase and for the 30-min dynamic study were generated followed by GFR calculation using Gate's method.

## Results

Out of a total of 62 consecutive patients with solid tumours there were 48 males and 14 females with

with a ratio of about 1 to 3 as shown in Figure 1. The mean age of the total patients was 55.5 ± 11.6 years with range of 26-70 years. The mean age for males and females was 55.83 years and 55.53 years with a range of 26-70 years and 45-70 years respectively as shown in Table 1.

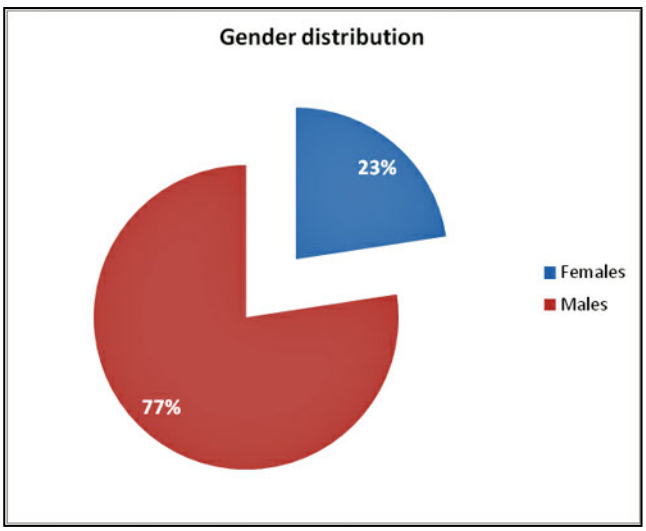


***Figure 1*** *Gender distribution of patients with solid tumours*

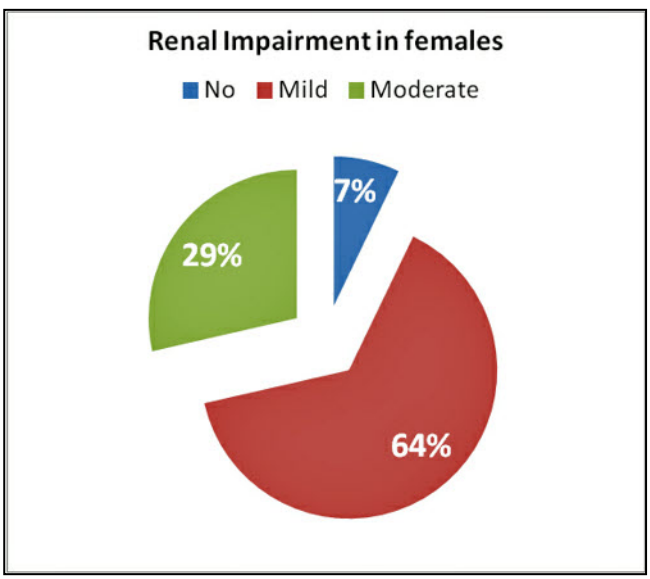


***Figure 2*** *Severity of renal impairment in female patients with solid tumours after cisplatin chemotherapy as evaluated by DTPA renal scan GFR*

***Table 1*** *Age distribution of patients with solid tumours*

| | Age | Mean | Median Age |
|---|---|---|---|
| Males | 26-70 | 55.83 | 59 |
| Female | 45-70 | 55.53 | 55 |

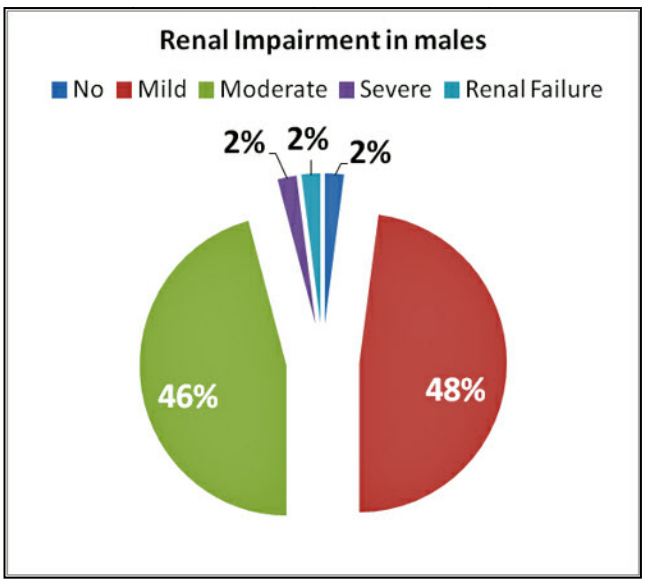


***Figure 3*** *Severity of renal impairment in male patients with solid tumours after cisplatin chemotherapy as evaluated by DTPA renal scan GFR*

The patients were stratified on the basis of National Kidney Foundation Guidelines for classification of Chronic Kidney Disease into normal, mild, moderate, severe renal impairment and renal failure on the basis of GFR measured by Gates method through DTPA renal scan after chemotherapy as shown in Table 2.

The mean GFR after completion of 6 cycles of chemotherapy was 60.13 ± 16.23 ml/min with a range 11-96 ml/min. Only 1.6% of the patients had severe cisplatin-induced renal

***Table 1*** *Distribution of patients on the basis of GFR on post chemotherapy renal scan*

| Patient Groups | GFR | No of patients | % of patients |
|---|---|---|---|
| No impairment | >90 | 2 | 3.2 % |
| Mild impairment | 60-89 | 32 | 51.6 % |
| Moderate impairment | 30-59 | 26 | 41.9 % |
| Severe impairment | 15-29 | 1 | 1.6 % |
| Renal Failure | < 15 | 1 | 1.6 % |

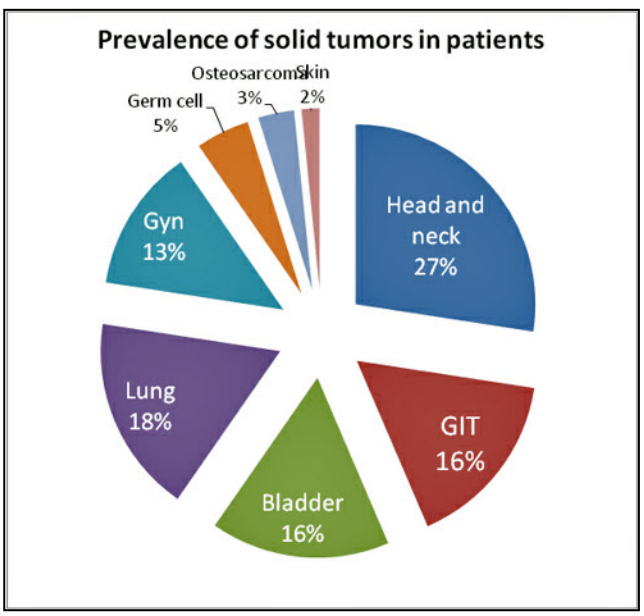


***Figure 4*** *Prevalence of solid tumours in patients*

renal injury in our study (GFR= 15-29 ml/min while 1.6% patients had severe renal injury, leading to renal failure (GFR <15 ml/min).

Out of a total of 14 female patients, 1 had no renal impairment , 9 had mild (mean reduction of GFR 14.14 ml/min) and 4 had moderate renal impairment (mean reduction of GFR 20.25 ml/min). 7% of female patients had no renal impairment (1/14), 64% had mild impairment (9/14) and 29% had moderate impairment (4/14) as shown in Figure 2.

In the case of male patients, out of a total of 48 patients, 1 had no renal impairment, 23 had mild renal impairment (Mean reduction of GFR 14.26 ml/min) , 22 had moderate renal impairment (Mean reduction of GFR 20.17 ml/min) while one each had severe renal impairment and renal failure. 2 % of male patients had no renal impairment (1/48), 48% had mild (23/48) and 46% had moderate renal impairment (22/48) respectively and 2% had severe renal impairment (1/48) and renal failure (1/48) each as shown in Figure 3.

The patients were also divided into various groups on the basis of their diagnosis at enrolment in the study as shown in Figure 4.

## Discussion

The importance of an early diagnosis of cancer lies in the need to identify the disease before it becomes so advanced so as to disallow mitigation without a consequence. Such early diagnosis programs are peculiarly important in resource constrained environments where the diagnosis is usually delayed and screening is often not available to everybody [9,10].

Chemotherapy remains the backdrop of modern antineoplastic therapy [11, 12]. Among the multitude, cisplatin stands out as the only anticancer drug that was empirically used for cancer treatment with success even before its mechanism of action was determined [13, 14]. However, early after its clinical use started in earnest, a number of physicians reported possible relation with renal dysfunction [3, 4,15]. As early as 1978, the flurry of published cases reporting cisplatin-induced renal damage necessitated a systematic review of these cases, which established a tangible connection between cisplatin administration and the subsequent renal dysfunction [16]. Since then, to date numerous other studies have borne out these ominous conclusions and a recent extensive literature review on medline indexed resources (Pubmed) revealed more than 40,000 publications on various aspects of cisplatn therapy with 998 publications specifically relating to cisplatin-induced renal injury. This is due to an extensive underlying interest in salvaging the role of cisplatin as a first line chemotherapeutic agent despite its nephrotoxic effects.

For the purpose of comparing our results, a literature review identified 6 studies from 1988 to 2013. In the first such retrospective study by Macleod *et al.* in 1988, the immediate and delayed effects of cisplatin on renal function were measured in patients with testicular tumours by evaluating $^{51}$Cr-EDTA clearance. Major differences in study design (versus our study) included a homogenous patient group, higher cumulative dose and a longer follow-up time. A 23% reduction in mean GFR was seen from 137 ml/min to 106 ml/min which was statistically significant [17]. The results were not significantly different from our study.

In a study in 1988, skinner *et al.* measured GFR in 35 children post cisplatin and found cisplatin-induced nephrotoxicity in 18 out of 31 patients. Their study population was comparable to our study population. It is however worth noting that a higher proportion of younger patients in their study had no nephrotoxicity as compared to our study (age range: 0.1-16.6 years *vs.* 26-75 years; proportion of patients without nephrotoxicity: 10/31 *vs.* 2/62, $p<0.001$). This suggests a favourable effect of younger age on cisplatin pharmacodynamics and renal physiology [18].

In 1999, Arndt *et al.* at Mayo clinic evaluated renal function in children and adolescent 3 months following completion of chemotherapy regimen comprising cisplatin in 24 patients with osteogenic sarcoma. It was shown that a higher mean age and cumulative dose of cisplatin, possibly translated into a lesser proportion of patients having a normal post cisplatin GFR [19] as seen in our patients. In 2011, *Mathe et al.* performed a retrospective analysis of cisplatin nephrotoxicity in 242 patients suffering from lung cancer. Cisplatin nephrotoxicity (established by >25% drop in GFR from pre treatment GFR measured by $^{99m}$Tc-DTPA clearance) was seen to be present in 7.5% (n=80) patients without any co-morbidity [20]. Finally, in a study by Sandur et al in 2013 comprising 197 patients, 58(29.4%) patients registered a more than 25% decrease in GFR as compared to baseline (29.4% vs 35.4% in our study). The difference in the proportion of patients with 25% or more GFR reduction between the two studies was not significant and the results were comparable (22/62, 35.4% vs. 58/197, 29.4%; p=0.45). The surprising similarity of results is possibly due to comparable age group of population under study (mean age; 54.5±9.6 vs. 55.5±11.6 in our study). This implies that age probably acts as an independent risk factor in cisplatin-induced nephrotoxicity [21].

## Conclusion

Since only 2/62 (3.2%) of the patients in our study developed severe renal injury at the completion of 6 cycles of cisplatin-based chemotherapeutic, this effectively demonstrates

the clinical efficacy and safety of cisplatin as an important anti-neoplastic drug due to low incidence of renal side effects. However, patients at risk of cisplatin-induced nephrotoxicity will probably benefit from an earlier diagnosis of incipient renal damage by DTPA renal scan leading to a timely discontinuation of this drug if indicated.

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