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Original Article

Oncology Section

Cisplatin Induced Renal Insufficiency Measured by Glomerular Filtration Rate with $_{99}$mTc-DTPA and by using Serum Creatinine based Formulae: A Prospective Study

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ABSTRACT

Introduction: Cisplatin also known as Cis-Diammine-Dichloroplatinum (CDDP) is a chemotherapeutic alkylating nephrotoxic agent. Thus, it is necessary to know if renal function is normal before starting chemotherapy. Glomerular Filtration Rate (GFR) can be assessed directly by using a radiopharmaceutical (dGFR). Estimated GFR (eGFR) method use, Serum Creatinine (SCR) levels in mathematical formulae such as Cockroft-Gault (CG) and abbreviated. Modified Diet in Renal Disease (aMDRD). The serum creatinine level is a function of GFR but is relatively insensitive for detecting early renal insufficiency.

Aim: We aimed to correlate the incidence of Renal Insufficiency (RI) before and one month after completion of chemotherapy treatment by various methods.

Materials and Methods: In this prospective study, we examined 64 patients with locally advanced head neck and uterine cervix cancers, before and one month after chemotherapy treatment with CDDP. Single agent CDDP was used with dose range between 35mg/m^2 as concurrent weekly chemotherapy.

Results: Baseline RI was seen in 9.3% of patients by SCR levels, in 21.8% by the dGFR method, in 43.75% by the GFR-CG method and in 25% by the GFR-aMDRD formula. We considered GFR of <60 ml/min and SCR >1.5mg% as RI. After completion of treatment, the median RI was seen in 12.5% by SCR levels, 34.38% by dGFR method, 53.13% by GFR-CG method and 40.63% by GFR-aMDRD formula.

None of the methods of GFR estimation showed statistically significant increase in RI one month after CDDP infusion. Only a weak correlation was seen between dGFR and eGFR based on SCR value (p=0.006).

Conclusion: Baseline RI was detected in 12% more cases when measured by dGFR as compared with SCR level. However, mathematical formulae overestimated baseline RI as compared to dGFR. One month after completion of treatment with CDDP chemotherapy, RI increased in 10%-15% cases as detected by all the four evaluated methods. There is weak correlation between SCR and dGFR thus implicating the importance of dGFR in assessing RI. Thus, despite normal SCR levels, GFR by radioisotope method should also be done as pre-treatment workup for cisplatin based chemotherapy.

Keywords: Chemotherapy, Nephrotoxicity, Radioisotope

INTRODUCTION

Cisplatin also known as Cis-Diammine-Dichloroplatinum (CDDP) is a chemotherapeutic alkylating nephrotoxic agent. Cisplatin is used as standard chemotherapy in concurrent setting in different sites like head and neck cancer, cervical cancer and other cancers [1,2].

Coughlin CT and Richmon RC and Douple EB suggested treatment efficacy of cisplatin by two mechanisms [3,4]. In cells, binding of platinum to DNA inhibits repair of sublethal damage as well as transcription of cytoplasmic proteins thus causing cytotoxic effects. In kidney, cisplatin is freely filtered as well as secreted by tubular cells. Acute toxicity is mainly reflected by proximal tubular dysfunction [5,6]. However, cisplatin induced acute nephrotoxicity is dose limited, but can be prevented with adequate hydration. There is a little doubt that repeated infusion of cisplatin may lead to chronic RI. However, according to the literature, kidney function seems to stabilize on a lower functional level with no or very little further deterioration after completion of chemotherapy [7-9]. Renal function may worsen with increasing age, co-morbities like diabetes and hypertension, acute loss of weight and muscle mass, dehydration and long term use of non-steroidal inflammatory drugs and after some malignancies like multiple myeloma [10,11]. Therefore renal function assessment is important and can be done by glomerular filtration rate using dGFR.

Such a method uses technetium-$_{99}$m-diethyl-triamine-penta-acetic acid ($_{99}$mTc-DTPA). In dGFR method $_{99}$mTc-DTPA is injected into the patient. It emits X-rays which are picked up by gamma camera and converted into electronic signals. These signals reflect renal functional status. Other methods are SCR levels and eGFR. The eGFR is calculated by indirect mathematical formulae such as CG [12-14] and aMDRD [15] which are based on SCR levels and patient's body weight, height, age and ethnicity.

Cockcroft-Gault (CG) formula:
CrCl (mL/min) = k x {(140 – age) x weight (kg)} / SCR (μ mol/L),

Where k = 1.23 (male) or 1.04 (female).

aMDRD formula:
GFR (mL/min/1.73m^2) = k x 186 x (SCR)-1.154 x (age)-0.203,

Where k = 1 (men) or 0.742 (women), GFR indicated glomerular filtration rate and SCR is measured in mg/dl.

In India, to the best of our knowledge, there is no prospective study that documents the incidence of RI before and after cisplatin infusion [16-20]. Therefore, we conducted a prospective study in patients who were planned to receive cisplatin with the aim to study the incidence of RI before and after CDDP and to correlate dGFR and eGFR.

MATERIALS AND METHODS

This prospective study was done in the Department of Radiotherapy and Nuclear Medicine at a tertiary care hospital between August 2013 to November 2015. Clearance was sought from the institutional ethics committee and all patients were required to sign informed consent form. We included histopathologically proven previously untreated 64 consecutive patients of locally advanced stage (III or IV) head and neck or uterine cervix cancers. Cisplatin based

concurrent chemoradiotherapy was planned for all patients. Prior to starting treatment, investigations for locoregional and metastatic status of disease, complete blood counts and liver function tests were done. Renal function tests with dGFR, SCR and eGFR using CG and aMDRD formulae were done before and one month after completion of treatment. Patients with metastatic disease, diabetes, previous renal irradiation, renal invasion by tumour or urinary tract obstruction, combination of Ifosfamide and baseline GFR 10-30ml/m were excluded from the study.

Renal Function Evaluation

Pre-treatment renal function was estimated by direct radioisotope measurement or indirectly by serum creatinine and estimated glomerular filtration rate using CG and aMDRD formulae.

SCR was measured by alkaline picrate method using modified Jaffe's kinetics with an autoanalyser. Plasma clearance of radio-isotope $_{99}$mTc DTPA was measured in nuclear medicine department as dGFR.

Radionuclide renography was done after intravenous injection of 3 mCi of $_{99}$mTc DTPA. Dynamic images were acquired in posterior projection for ten minutes. Region of interest were drawn on both kidneys and background GFR was estimated by gate technique. CG formula and the aMDRD disease formula were used to calculate eGFR.

After one method of treatment completion, renal function was assessed in the form of SCR level, eGFR using both CG and aMDRD formula and by radioisotope method. Renal function reported by either direct or indirect method was staged according to clinical practice guideline published by working group of the National Kidney Foundation as below-

Stage 1, GFR ≥ 90 mL per minute;

Stage 2, GFR from 60 to 89 mL per minute;

Stage 3, GFR from 30 to 59 mL per minute;

Stage 4, GFR from 15 to 29 mL per minute; and

Stage 5, GFR <15 mL per minute.

GFR below 90ml per minute has been considered as abnormal according to the Kidney Disease Outcome Quality Initiative (K/DOQI) – Kidney Disease Improving Global Outcome (KDIGO) official international definition of RI [15]. However, in our study RI was considered as a GFR <60ml/min SCR value of > 1.5mg/ml was considered as RI [17-20].

Chemotherapy: Cisplatin was administered at dose of 35mg /m^2 weekly with the use of hyper-hydration and forced diuresis. In case of stage 3 RI, dose of cisplatin was reduced by 25%.

Radiotherapy: Patients were simulated in computed tomography simulator with thermoplastic immobilization device for head and neck patients and positioning device such as knee rest for carcinoma of cervix to reproduce same position during treatment. Three dimensional conformal radiotherapy was planned using Monaco treatment planning system (version 5.0). Radiation was delivered by linear accelerator with 6 or 10 MV photons. Three field technique was used in head and neck cancer (2 parallel and opposite and a low anterior neck field) and four conformal field was used in carcinoma of cervix. Adequate coverage of target volumes and sparing of organs at risk was achieved. Treatment verification with Electronic Portal Imaging Devices (EPID) was done.

STATISTICAL ANALYSIS

Comparison of RI before treatment and after treatment was done using Chi-square test and correlation between various methods was done using correlation coefficient (r).

RESULTS

A total 64 patients were enrolled in our study. Among all patients 42 were male and 22 were female, M:F ratio was 1.9. Patients were of only five sites. Most of the patients were. of carcinoma of oropharynx. As concern with age, weight and height median was 53 years ranges from 34-70, 58 kg ranges from 41-82 and 160 cm ranges from 148-184 respectively [Table/Fig-1]. Baseline prevalence of renal insufficiency was seen in 9.3% by serum creatinine levels, 21.8% by dGFR method, 43.75% by CG method and 25% by aMDRD formula. After completion of treatment, the median renal insufficiency was seen in 12.5% by serum creatinine levels, 34.38% by dGFR method, 53.13% by CG method and 40.63% by aMDRD formula [Table/Fig-2]. Only a weak or mild correlation was seen between dGFR and calculation of GFR based on SCR value [Table/Fig-3].

DISCUSSION

As reported in various studies, there is significantly lower GFR in Indian population compared with western population [11,16-20]. We considered a lower normal cut-off value for dGFR/ eGFR<60ml/min and SCR value of >1.5mg/ml as RI [16-20]. Baseline renal insufficiency in patients with malignancy detected by raised serum creatinine was 9.37% cases while abnormal dGFR, CG and aMDRD were found in 21.88%, 43.75% and 25.00% cases respectively.

Patient characteristics	Total number of patients (n=64)
Male	42
Female	22
Median age (range)	53 (34-70) years
Median weight (range)	58 (41-85) kg
Median height (range)	160 (148-184) cm
Site of malignancy Oral cavity Oropharynx Hypopharynx Larynx Cervix	 11 17 12 9 15
Median (range) number of weekly cisplatin cycles	6 (4-7)
Median (range) dose of cisplatin	50(40-50) mg

[Table/Fig-1]: Patient and tumour characteristics.

	Level of correlation	(Correlation coefficient) r	p-value
Serum Creatinine – dGFR*	Weak/No	0.025	0.842
Serum Creatinine – GFR-CG†	Moderate	-0.667	<0.001
Serum Creatinine – GFR-aMDRD‡	Strong	-0.784	<0.001
dGFR – GFR-CG	Weak/No	0.169	0.183
dGFR – GFR-aMDRD	Weak/No	-0.107	0.398
GFR-CG – GFR-aMDRD	Strong	0.717	<0.001

[Table/Fig-2]: Correlation of pre-treatment variables.
Abbreviations: *dGFR, direct method of GFR measurement by radionuclide; GFR-CG†, calculated GFR by Cockroft-Gault formula; a MDRD‡, calculated GFR by abbreviated modified of diet in renal disease.

	Level of correlation	Correlation coefficient r	p-value
Serum Creatinine – dGFR*	Mild	0.338	0.006
Serum Creatinine – GFR-CG†	Mild	-0.484	<0.001
Serum Creatinine – GFR-aMDRD‡	Strong	-0.829	<0.001
dGFR – GFR-CG	Mild	0.481	<0.001
dGFR – GFR-aMDRD	Mild	-0.335	0.007
GFR-CG – GFR-aMDRD	Moderate	0.676	<0.001

[Table/Fig-3]: Correlation of variables after treatment completion.
Abbreviations: dGFR*, direct method of GFR measurement by radionuclide; GFR-CG†, calculated GFR by Cockroft-Gault formula; aMDRD‡, calculated GFR by abbreviated modified of diet in renal disease.

One month after treatment completion with cisplatin serum creatinine was found to be abnormal in 12.50% cases while dGFR, CG and aMDRD were found to be abnormal in 34.38%, 53.13% and 40.63% cases.

It was seen that proportion of cases with abnormal SCR levels and abnormal glomerular filtration rate (iso, CG, MDRD) was found to be higher after treatment as compared to before treatment. RI increased after CDDP chemotherapy in 10-15% of patients as reflected by all methods of GFR estimation. Discrimination between serum creatinine level and GFR value measurement had been well studied [21]. It has been documented that by the time serum creatinine rises >1.5mg/dl, GFR may fallen by 40% [9-12].

The degree of renal damage due to CDDP was categorized according to RIFLES (risk, injury, failure, loss, end stage renal disease) criteria for acute tubular injury [22]. So most commonly used parameter, serum creatinine level for renal insufficiency seems to be less sensitive therefore, there should be a tool or method which can assess renal status. GFR measure by radioisotope method is a widely accepted method.

However the cost, time and nuclear medicine facility requirement are limitations for developing countries. Among various mathematical formulas investigated, most accepted are Cockroft-Gault and abbreviated modified of diet in renal disease method. Between two mathematical formulas our study showed aMDRD better correlated as compare to CG formula and by literature also [9,10].

Perhaps the frequency of RI is underestimated in routine clinical practice, because mostly SCR measurements are done to know the RI. Since SCR is not interpreted together with the gender, age and weight of the patient, it may not be an appropriate tool. As a limitation of our study serum creatinine was measured by alkaline picrate method using modified Jaffe's kinetics with an autoanalyser. The ideal method for creatinine estimation would have been enzymatic, but there are many studies done and published recently which have used compensated Jaffe's method. Moreover, the Jaffe's methods are most commonly commercially used assay in clinical laboratories. These parameters (age, weight and gender) represent the muscle mass of the patient and the creatinine production rate [9]. As reported age, diabetes and hypertension impact significantly on baseline renal function [15]. Effect of patient and treatment related factors on the renal functional status before and after total dose of cisplatin needs to be evaluated in a larger prospective study. Before infusion of cisplatin based chemotherapy, it is safer to confirm eGFR by dGFR especially in elderly patients or in whom SCR levels are borderline higher value.

CONCLUSION

When measured by dGFR baseline RI was detected in 12% more cases as compared with serum creatinine level. However mathematical formulae overestimated baseline RI as compared to dGFR. One month after completion of treatment with CDDP chemotherapy, RI increased in 10%-15% cases as detected by all the four evaluated methods.

There is weak correlation between SCR and dGFR thus implicating the importance of dGFR in assessing RI. Thus despite normal serum creatinine levels, GFR by radioisotope method should also be done as pretreatment workup for cisplatin based chemotherapy.

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