Estimating glomerular filtration rate in oncology patients receiving Cisplatin chemotherapy: Predicted creatinine clearance against $^{99m}$Tc-DTPA methods

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Abstract. The therapeutic potential of cisplatin as the best anticancer treatment for solid tumor is limited by its potential nephrotoxicity. This study analyses the incidence of cisplatin induced nephrotoxicity in oncology patients through GFR estimation using $^{99m}$Tc-DTPA plasma sampling (reference method) and to compare with predicted creatinine clearance and Tc-99m renal scintigraphy. A prospective study of 33 oncology patients referred for GFR estimation in Penang Hospital. The incidence of cisplatin induced nephrotoxicity was analysed via radionuclide and creatinine based method. Of 33 samples, only 21 selected for the study. The dose of cisplatin given was 75 mg/m$^2$ for each cycle. The mean difference of GFR pre and post chemotherapy (PSC) 2 was 13.38 (-4.60, 31.36) ml/min/1.73m$^2$ (p 0.136). Of 21 patients, 3 developed severe nephrotoxicity (GFR < 50ml/min/1.73 m$^2$) contributing 14.3% of incidence. Bland-Altman plot showed only PSC 1 is in agreement with PSC 2 technique. Intraclass Correlation Coefficients (ICC) also showed that PSC 1 has high degree of reliability in comparison to PSC 2 (p < 0.001). The other methods do not show reliability and agreement in comparison to PSC 2 (p < 0.05). 3 of 21 patients (14.3%) developed severe nephrotoxicity post cisplatin chemotherapy. This percentage is much less than the reported 20 – 25% of cases from other studies, probably due to small sample size and biased study population due to strict exclusion criteria. Radionuclide method for evaluating GFR is the most sensitive method for the detection of cisplatin induced nephrotoxicity by showing 3 of 21 patients developing severe nephrotoxicity. PSC 1 was found to be a reliable substitute of PSC 2. The other methods are not reliable for detection of early nephrotoxicity. We will recommend the use of single plasma sampling method (PSC 1) for GFR estimation in monitoring post cisplatin chemotherapy patients.

1. Introduction

Cisplatin remains as one of the best anticancer agent for the treatment of solid tumour over the last 30 years [1]. Despite its well-known desirable effect on cancer treatment per se, its full therapeutic potential has been limited by its potential toxicity. Many articles reported that the incidence of nephrotoxicity following high dose cisplatin chemotherapy happens in the range of 20 to 25% [2, 3]. Therefore, current clinical practice requires close monitoring of the kidney function pre and post chemotherapy to anticipate any significant decline of renal function. Therefore, estimating the glomerular filtration rate (GFR) has been accepted at large as a parameter to represent the functional status of the kidney [4]. There are various techniques which has been proposed to estimate GFR...
using endogenous or exogenous markers, but the most important aspect in choosing which method to use will have to take into account the simplicity, cost and availability without compromising the accuracy of the result.

2. Materials and Methods
This is a prospective study involving Nuclear Medicine Department and Radiotherapy and Oncology Department in Hospital Pulau Pinang. The sample is derived using PS Power and Sample Size Ver. 3.0.10 using paired t-test. 21 subjects with various solid tumors referred for GFR evaluation (16 males and 5 females, mean age 55.1) were enrolled in this study. The inclusion criteria include cases for high dose cisplatin. Those with comorbidities or GFR < 60 ml/min/1.73m² were excluded from the study. GFR was calculated for each subject by plasma two samples clearance method (PSC 2), plasma one sample clearance method (PSC 1), Gates method, predicted creatinine clearance by modified diet in renal disease (MDRD) method and Cockroft-Gault (CG) method at prechemotherapy (3 days prior to start of cisplatin) and within 3 days to 1 week at post completion of chemotherapy cycles.

2.1. Gates and PSC Methods
Tc-99m DTPA is prepared using a commercially available freeze-dried kit (Eczacibasi Monrol Nükleer Ürünler San, Turkey). Two sets of radiopharmaceuticals are prepared in the range of 185MBq to 250MBq. One of the radiopharmaceutical is set aside as the standard, while the other one is used for patient dose. The injection dose and the standard dose are calibrated in a dose calibrator. The percent difference between the dose and the standard should not exceed 5% under any circumstances. The whole Tc-99m DTPA injection dose is injected into the patient at the start of the renal scintigraphy study and the time is recorded. After injection, the syringe is assayed and any residue will be recorded. If the residue in the syringe post injection is >3% of the dose, an appropriate correction in the calculation should be made. The patient then undergoes renal scintigraphy using the gamma camera. The GFR (GFR Gates) is automatically estimated by a commercially available computer software (E.Soft 2.0 GHz Siemens Medical Solutions USA Inc.) according to the Gates’ algorithm.

In two samples method, 10 ml of blood sample is taken at 60 and 180 minutes after the radiopharmaceutical injection, and in one sample method, only single sample drawn at 180 minutes from the opposite arm into an EDTA collection tube and the time is recorded. The blood should be mixed well with anticoagulant. Blood samples are centrifuged at 1000 grams for 10 minutes to separate the red blood cells from the plasma. 100 microliter aliquot of plasma will be pipetted into a plain tube labeled as plasma sample. The counts should be taken from the 3 tubes using gamma well counter, which consists of plasma sample tube, standard solution (1:10000 dilution) and blank test tube containing 100 microliter of distilled water for the purpose of background correction. Counts were obtained for 1 minute from each tube in an automatic gamma well counter (Biodex Atomlab 950 Uptake Stand). The activity of each tube will be recorded automatically and GFR value will be calculated automatically as well by the computer system.

2.2 Predicted creatinine clearance
The GFR (GFRMDRD) was predicted from the serum creatinine (SCr) level using MDRD study using equation (1) from [5]. The GFRMDRD is multiplied with a factor of 0.742 if female and 1.212 if African American.

\[
\text{GFRMDRD} = 186 \times (\text{SCr (umol/L)})^{1.154} \times (\text{Age})^{0.203}
\]

The GFR (GFRCG) was predicted from the serum creatinine (SCr) level using Cockroft-Gault’s equation (2) where Constant is 1.23 for men and 1.04 for women [6].
\[ \text{GFRCG} = \frac{(140 - \text{Age}) \times \text{Mass (kg)} \times \text{Constant}}{\text{Serum Creatinine (umol/L)}} \quad (2) \]

The GFR (GFRCKD-EPI) was predicted from the serum creatinine (SCr) level using CKD-EPI equation (3) from [7]. GFRCKD-EPI is multiplied with a factor of 1.018 if female and 1.159 if African American.

\[ \text{GFRCKD-EPI} = 141 \times \min \left( \frac{\text{SCr}}{\kappa}, 1 \right)^{2} \times \max \left( \frac{\text{SCr}}{\kappa}, 1 \right)^{1.209} \times 0.993^{\text{Age}} \quad (3) \]

3. Data Analysis and Statistics
The sample is derived using PS Power and Sample Size Ver. 3.0.10 using paired t-test. The required size to achieve a power of 80% and confidence interval of 95% is 33 patients. The demographic, clinical, GFR from serum creatinine and the 99mTc-DTPA methods are recorded in the data collection sheets and analysed using Statistical Package for Social Science (SPSS) software version 21.0.0. GFR values obtained from pre and post chemotherapy were normalised according to body surface area. Mean GFR calculated for each method (CG, MDRD, CKD-EPI, Gates, PSC 1 and PSC 2). Paired t test was performed to obtain mean difference of GFR pre and post chemo. Test was significant at p value of < 0.05. Scatter plot was used to correlate between each different method. Intraclass Correlation Coefficients was used to assess reliability of all methods in comparison to PSC 2.

4. Results
The patients are given high dose cisplatin (75 mg/m²) for every cycle of chemotherapy. Out of 21 patients, 3 developed severe nephrotoxicity (GFR < 50ml/min/1.73m²). PSC 2 (reference method) estimated the mean fall in GFR of 13.38 (-4.60, 31.36) ml/min/1.73m² (p 0.136). The other methods showed mean fall in GFR as 7.03 (2.43, 11.63), 6.70 (0.02, 13.38), 0.86 (-5.65, 7.36), 7.55 (0.75, 14.34) and 20.30 (6.45, 34.15) ml/min/1.73m² as estimated by CG, MDRD, CKD-EPI, Gates and PSC 1 respectively (Figure 1). We observed that the GFR declined post chemotherapy by all methods.

![Figure 1. Difference in GFR value according to different methods pre and post cisplatin chemotherapy.](image-url)
Table 1. Detection of nephrotoxicity post chemotherapy by all methods.

| Methods | No. of Cases Detected | Percentage (%) of patients developing nephrotoxicity (n = 21) |
|---------|------------------------|---------------------------------------------------------------|
| CG      | 1                      | 4.8                                                           |
| MDRD    | 0                      | 0.0                                                           |
| CKD-EPI | 0                      | 0.0                                                           |
| Gates   | 4                      | 19.0                                                          |
| PSC 1   | 3                      | 14.3                                                          |
| PSC 2   | 3                      | 14.3                                                          |

The table above shows the number of cases developing nephrotoxicity post completion of chemotherapy. In this study, Gates method showed the highest percentage of case detection (19%) as compared to other methods. This is followed by PSC 1 and PSC 2 whereby both methods’ detection rate at 14.3% followed by the CG method (4.8%). The MDRD and CKD-EPI methods are unable to detect any evidence of nephrotoxicity in this study. Thus, from this observation we may conclude that MDRD and CKD-EPI are not sensitive in the measurement of changes in GFR and the detection of nephrotoxicity post chemotherapy.

Figure 2. The Bland-Altman plot of 99mTc-DTPA for GFR (n=21) comparing between PSC 2 and PSC 1 methods.

The Bland-Altman analysis indicates that the 95% limits of agreement between PSC2 and PSC 1 methods is narrow ranging from -15.9 to 6.6. The scatter plots is also more consistent and close to the line across the graph. The rest of the methods showed inconsistent plot and away from the line across the graph. Hence, we may conclude that PSC 1 and PSC 2 are in agreement with each other (Figure 2).
Table 2. Intraclass Correlation Coefficients (ICC)

|                   | Intra-class Correlation Coefficients | (95% CI)          | P value |
|-------------------|--------------------------------------|-------------------|---------|
| PSC2 – Cockroft-Gault | 0.085                                | (-0.350, 0.490)   | 0.353   |
| PSC2 - MDRD       | -0.063                               | (-0.473, 0.369)   | 0.610   |
| PSC2 – CKD Epi    | 0.101                                | (-0.336, 0.502)   | 0.328   |
| PSC2 - Gates      | 0.171                                | (-0.271, 0.554)   | 0.223   |
| PSC2 – PSC1       | 0.696                                | (0.388, 0.864)    | <0.001  |

From the ICC, a high degree of reliability in measuring GFR was found between PSC 1 in comparison to PSC 2 method which shows a significant p value of less than 0.001 and a 95% confidence interval from 0.338 to 0.864 (p < 0.05, CI 0.338, 0.864). The rest of the methods showed insignificant result and do not show reliability in measuring GFR in comparison to PSC 2 method.

5. Discussion

Our mean age of respondents is 55.1 years (10.80). This represents the majority of our patients are within the middle-aged group. Increasing age physiologically will lead to reducing GFR level [8]. Since cancer risk is also increasing with increasing age, therefore renal resistance towards cisplatin will also be reduced as age increases [9].

Upon completion of 3 cycles of chemotherapy, the average decline in GFR was 13.38 (-4.60, 31.36) ml/min/1.73m². This shows 14% reduction from baseline GFR and is much less than the reported average declines in GFR post completion of chemotherapy by Fatima N. [10], which showed 43.86 ± 16.10 ml/min/1.73m² reduction. This factor can be explained by the difference in the completion of chemotherapy cycle itself as we only conducted up to 3 cycles of high dose cisplatin as compared to 6 cycles of cisplatin in the former study with higher average cumulative dose. The concept of cisplatin induced nephrotoxicity is based on repetitive exposure and the effect is cumulative and dose dependent [3]. Therefore we may conclude that the more cycle of cisplatin and the higher is the cumulative dose, the more likelihood for cisplatin induced nephrotoxicity to occur.

The creatinine based methods as shown by many studies do not correlate with the radionuclide methods. CG underestimated GFR as much as 14% whereas MDRD underestimated GFR by 10% in comparison to PSC 2 [10]. The reasons are probably attributable to inaccuracies of formulae secondary to intra-assay and intra-individual variability from serum creatinine and GFR values, lack of calibration of serum creatinine result in laboratories as well as measurement of other variables in predicted equations affecting the precision and accuracy of renal clearance prediction equations [11]. From our result, Gates method detected the highest number of cases for cisplatin induced nephrotoxicity by giving the highest percentage of 19.0%. The next lower percentage of patients developing nephrotoxicity is followed by PSC 1 and PSC 2 method by giving 14.3% each. CG method showed only 1 case by giving percentage of 4.8%. MDRD and CKD-EPI showed the worst detection rate and was the least sensitive by not having any case detection at all. Gates appears to have the highest case detection than the reference method itself. Since Gates was found to give the highest underestimation of GFR (23% in this study), this maybe a false positive result leading to falsely high percentage of case detection. The other creatinine based methods do not show good detection of cases and is thus least sensitive of all methods conducted here. This maybe attributable to the fact that serum creatinine tends to underestimate GFR and creatinine will not be raised until the kidneys lost 60% of its total function [12].
In conclusion, utilisation of radionuclide methods has shown better detection in GFR changes compared to creatinine based techniques. Finally, we will recommend the use of one plasma sampling method (PSC 1) for GFR estimation in monitoring post cisplatin chemotherapy patients. In comparison to other study, the findings of this study show similar trend with all methods; radionuclide methods are superior in detecting early GFR changes than creatinine based techniques [10].

6. References
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