SERIAL-MEASURED VERSUS ESTIMATED CREATININE CLEARANCE IN PATIENTS WITH NON-SMALL CELL LUNG CANCER RECEIVING CISPLATIN-BASED CHEMOTHERAPY

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Background and Purpose: Cisplatin-based chemotherapy is the main therapy for patients with advanced stage non-small cell lung cancer (NSCLC). The dose of cisplatin is adjusted according to the patient’s renal function. Calculation of creatinine clearance (CCr) by 24-hour urine collection is the most common method for estimating the glomerular filtration rate but is time-consuming and inconvenient. Estimation of CCr using the Cockcroft-Gault formula has been suggested to be accurate, reproducible, and less costly. This study compared CCr values obtained by measured and estimated methods during cisplatin-based chemotherapy in NSCLC patients in Taiwan.

Methods: A total of 92 patients (58 men, 34 women) with advanced NSCLC who completed 6 cycles of chemotherapy participated in the study. The dose of cisplatin per cycle was 80 mg/m² every 28 days, reduced to 50 mg/m² if CCr was 30 to 60 mL/min by the measured method. When urine collection was finished, serum and urine creatinine levels were measured simultaneously. Estimated values were calculated before each cycle of chemotherapy.

Results: The mean measured CCr was 85.2 mL/min, 25.7 mL/min higher than the mean estimated value. CCr values obtained by both methods were significantly reduced during the 6 cycles of chemotherapy. There was no significant difference in CCr values between patients aged < 65 years or ≥ 65 years (-19.9 vs -15.1 mL/min, p = 0.15). Using a cut-off of measured CCr ≥ 60 or < 60 mL/min, agreement on the dosage for both methods was 51% for all patients, 77.7% for patients < 65 years, and 26.7% for patients ≥ 65 years.

Conclusions: The Cockcroft-Gault formula underestimated measured CCr by about 25 mL/min in this study. Cisplatin-based chemotherapy reduced CCr, with no significant difference between older and younger patients. Use of the estimated method would result in significant under-dosing, especially for patients ≥ 65 years old.

Key words: Carcinoma, non-small-cell lung; Cisplatin; Creatinine


Early clinical trials with cisplatin encountered serious toxicity, mainly severe nausea, vomiting, neurotoxicity, ototoxicity, and nephrotoxicity. Initial experience has shown that about 25% of patients who received a single dose of cisplatin suffered reversible azotemia for 1 to 2 weeks following treatment.1 Irreversible renal failure requiring dialysis has also been reported, especially with large doses or multiple courses of treatment.2

There is evidence that the therapeutic efficacy of cisplatin increases with increasing dose.3 However, cisplatin-induced nephrotoxicity has also been shown to be dose-related in both animals and humans, as the kidney is the primary excretory organ for cisplatin.4 Several studies have reported changes in serum creatinine despite the administration of high-dose cisplatin and the reduction of creatinine clearance (CCr).5,5

Because the nephrotoxicity of cisplatin is dose-related and cumulative, early recognition of renal injury is needed for the safe and effective use of this agent. A normal or nearly normal (> 50 mL/min) baseline CCr is believed to be necessary for the avoidance of nephrotoxicity.8 Measured CCr was the most popular clinical method for accurately estimating the glomerular filtration rate.7-8 Previously, most cisplatin-based chemotherapy trials assessed patient eligibility using a pre-therapy 24-hour urine collection for CCr, even though it is inconvenient and possibly inaccurate if done without careful urine collection.10
The estimation of CCr using a formula derived by Cockcroft and Gault\textsuperscript{13} has been suggested to be more accurate and reproducible and less costly than a measurement based on 24-hour urine collection before cisplatin therapy.\textsuperscript{12} In recent years, this method of estimation has gained popularity in international trials of cisplatin-based chemotherapy.

The purpose of this study was to compare the CCr values obtained by the measured and estimated methods during the course of cisplatin-based chemotherapy in non-small cell lung cancer (NSCLC) patients in Taiwan. We sought to determine whether the estimated method would predict the appropriate renal classification based on comparison with the measured method using a cut-off CCr value of \(60\) mL/min, and whether the drug dosage could be used to obtain accurate estimates of measured CCr.

**Methods**

We studied 92 patients (58 men, 34 women) with advanced NSCLC who completed 6 cycles of chemotherapy with gemcitabine and cisplatin from January 1999 to January 2001 at Taichung Veterans General Hospital. All patients had measured \(\text{CCr} \geq 60\) mL/min before the first cycle of chemotherapy. The cisplatin dose per cycle was \(80\) mg/m\(^2\) every 28 days.

Before treatment, all patients were without clinical evidence of severe systemic diseases, and they had received no diuretics or medications known to interfere with creatinine secretion (cimetidine and trimethoprim-sulfamethoxazole) or creatinine measurements (androgens, ascorbic acid, cephalothin, cefoxitin, levodopa, methyldopa, and high-dose penicillin). Body weight was measured before each cycle of chemotherapy.

To obtain the measured CCr value, urine was collected for 24 hours, with start and finish times recorded by nurses. When the urine collection was finished, serum and urine creatinine levels were measured simultaneously in all patients before chemotherapy. In all, there were 6 measurements for each patient before every chemotherapy treatment. If the measured \(\text{CCr} \geq 60\) mL/min, cisplatin \(80\) mg/m\(^2\) was given. If the measured \(\text{CCr} = 30\) to \(60\) mL/min, the dose of cisplatin was reduced to \(50\) mg/m\(^2\), as modified from Patterson and Reams.\textsuperscript{13} The Cockcroft-Gault formula for estimation is as follows:

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[(140 - \text{age}) \times \text{weight (kg)}] / [72 \times \text{serum creatinine (mg/dL)}] = \text{CCr (15\% less in females)}.
\]

Statistical analysis was performed using the Statistical Package for Social Sciences statistical software (SPSS standard version 8.0; SPSS Inc., Chicago, IL).

The patients were divided into 2 groups. One group was composed of patients < 65 years old and the other group was composed of patients \(\geq 65\) years old. We compared the CCr values between the measured and estimated (Cockcroft-Gault) methods of both groups using the paired \(t\)-test. Male versus female CCr values, obtained by both the measured and estimated methods, were compared with the Student’s \(t\)-test. The McNemar chi-squared test was used to compare the correct dosage between the measured and estimated methods in all patients with a cut-off value of measured \(\text{CCr} \geq 60\) or < \(60\) mL/min. We used the analysis of variance (ANOVA) test with repeated measures to determine differences between the CCr values from the first to the sixth cycle of chemotherapy. After ANOVA test was used to determine significance, Scheffe’s method was applied for post hoc comparison. We also compared the decrease in CCr values from the first to the sixth cycle of chemotherapy between those patients \(\geq 65\) and < 65 years old with the Wilcoxon rank sum test. A \(p\)-value < 0.05 was considered statistically significant. Simple linear regression was used to examine the association between the measured and estimated methods.

**Results**

There were 58 male patients with a mean age of 63.8 years; 21 of them were < 65 years old and 37 were \(\geq 65\) years old. The 34 female patients had a mean age of 58.2 years; 22 of them were < 65 years old and 12 were \(\geq 65\) years old. The mean values of the measured CCr of the male and female patients were 86.7 \(\pm\) 25.3 and 82.6 \(\pm\) 24.2 mL/min, respectively (\(p = 0.06\)). The mean values of the estimated CCr of the male and female patients were 55.1 \(\pm\) 17.6 and 67.1 \(\pm\) 16.7 mL/min, respectively (\(p < 0.01\)). After matching the age of each male and female patient, the differences of both the estimated and the measured CCr were not significant (\(p = 0.425\) and \(p = 0.438\), respectively).

The CCr values of patients < 65 years old were significantly higher than those of patients \(\geq 65\) years old with both methods (measured CCr 95.5 \(\pm\) 27.7 vs 75.8 \(\pm\) 17.6 mL/min, respectively [\(p < 0.01\)]; estimated CCr 71.7 \(\pm\) 17.2 vs 48.4 \(\pm\) 10.5 mL/min, respectively [\(p < 0.01\)]).

The CCr values were significantly lower with the estimated method for all patients (85.2 \(\pm\) 25.0 vs 59.5 \(\pm\) 18.2 mL/min, \(p < 0.01\)), and for both groups of patients (< 65 years old, 95.5 \(\pm\) 27.7 vs 71.7 \(\pm\) 17.2 mL/min, \(p < 0.01\); \(\geq 65\) years old, 75.8 \(\pm\) 17.6 vs 48.4 \(\pm\) 10.5 mL/min, \(p < 0.01\)).

The distribution and relationship of the measured and estimated CCr was plotted and revealed that most
However, 13.4% of patients ≥ 65 years old versus only 5.4% of patients < 65 years old had measured CCr values < 60 mL/min \( (p < 0.01) \).

Using a cut-off value of measured CCr at ≥ 60 or < 60 mL/min, agreement on the dosage of chemotherapy agents between the measured and estimated methods before the first cycle of chemotherapy was 66.3% for all patients, 93.0% for patients < 65 years old, and 40.8% for patients ≥ 65 years old (Table 2). There was a significant difference in dosage agreement between the 2 methods during the 6 cycles of chemotherapy in all patients, patients ≥ 65 years old, and patients < 65 years old (Table 3).

Linear regression analysis of the association between the measured and estimated methods \( (Y = a + bX, \text{ where } Y \text{ corresponds to measured CCr and } X \text{ corresponds to estimated CCr}) \), yielded \( Y = 29.459 + 0.936X \) \( (r = 0.684, p < 0.01) \) for all patients; \( Y = 30.760 + 0.930X \) \( (r = 0.553, p < 0.01) \) for patients ≥ 65 years old; and \( Y = 21.921 + 1.026X \) \( (r = 0.636, p < 0.01) \) for patients < 65 years old.

**Discussion**

If the methods of the international cisplatin-based chemotherapy clinical trials had been used to assess eligibility with the Cockcroft-Gault formula for estimation of CCr using a value ≥ 60 mL/min, then 59.2% of our patients ≥ 65 years old would have been excluded from the trials despite being able to tolerate the 6 courses of cisplatin-based chemotherapy with only mild renal toxicity. For this group of patients, the correct dosage would have been estimated for only 26.7%. Thus, the Cockcroft-Gault formula...
underestimated the measured CCr, resulting in an inadequate dosage for these patients.

The gender ratio and age distribution was similar to our previous survey of all NSCLC patients. Data on measured CCr values were incomplete because most of the patients could not complete the 6 courses of cisplatin-based chemotherapy due to disease progression. A small number of the patients discontinued the cisplatin-based chemotherapy because of gastrointestinal tract side effects or cisplatin-induced nephrotoxicity. Further study is needed to analyze all types of patients receiving cisplatin-based chemotherapy, as this study only included those patients who completed the 6 cycles of chemotherapy.

There are several possible reasons why the Cockcroft-Gault formula underestimated the CCr in this study. First, we used the Jaffé method to measure creatinine. This method is known to overestimate the serum level of creatinine by 5 to 15% because of a reaction with non-creatinine chromogens in serum.14 As this overestimated creatinine value is used in the denominator of the Cockcroft-Gault formula, the CCr value would be correspondingly lower. Second, Taiwanese patients are usually smaller and lighter than American people, while the lean body mass percentage is higher in Asian people.15 These differences imply that Taiwanese patients with the same body weight as Americans should have higher CCr values. Two additional causes may also have further contributed to the underestimation of the CCr of the elderly patients. First, it is well known that renal function decreases physiologically with age. CCr was found to decrease by 10 mL/min/1.73 m² every 10 years, beginning at age 30.16 However recently, several groups of researchers have documented that reduction of renal function in healthy elderly is considerably less severe than assumed in the past.17-19 Second, elderly patients seem to exist in a state of mild dehydration. Total body water as a percentage of body mass decreases steadily with age.20 This leads to further increase in the percentage of lean body mass, which is usually underestimated in elderly.

Little information is available on the influence of old age in cisplatin nephrotoxicity. Hrushesky et al investigated the reduction in the 24-hour CCr measurement after a mean of 6.9 doses of chemotherapy, including cisplatin at a dose of 60 mg/m² in patients 29 to 77 years old.21 CCr decreased 29 mL/min in patients < 50 years old, but only 16 mL/min in patients > 70 years old. The renal toxicity of cisplatin does not increase with age. Similar to our findings, a study by Thyss et al reported that for 35 patients older than 80 years, the mean decrease in CCr was 9.6 mL/min.22 Our study showed that the measured decrease was 15.1 mL/min for patients 65 years or older, and 19.9 mL/min for patients under 65 years old, with no significant difference.

Two hypotheses have been proposed to explain the relative protection against nephrotoxicity observed in elderly patients. First, during aging, the external medullary substance of the renal cortex is relatively preserved.23 The external medullary zone seems to be the site of maximal cisplatin concentration. Second, the overall renal concentration capacity for cisplatin is reduced in older individuals, and so the renal toxicity decreases.24

On the other hand, Hargis et al found age over 60 to be an important risk factor for the development of significant genitourinary toxicity during cisplatin treatment.25 Our patients did not develop symptoms of severe renal toxicity, as we reduced the dosage of cisplatin according to the measured CCr values. More patients 65 or older would have to reduce their dosage than those under 65 as elderly patients have lower baseline CCr values.

The clinical performance of an equation is more important for patient care than the equation’s mathematical predictive performance. Imprecision can be acceptable if the correct drug dosage is still chosen for the majority of patients. But in this study, the Cockcroft-Gault formula usually underestimated the CCr values, and could not substitute for the measured method in our patients.

### Table 3. Agreement of measured and estimated creatinine clearance (CCr) for dosage calculation in all completed courses of chemotherapy.

<table>
<thead>
<tr>
<th></th>
<th>All courses of chemotherapy</th>
<th>Courses of chemotherapy</th>
<th>Courses of chemotherapy</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(n = 552)</td>
<td>≥ 65 years old</td>
<td>&lt; 65 years old</td>
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<tr>
<td></td>
<td>Estimated CCr (mL/min)</td>
<td>(n = 288)</td>
<td>(n = 264)</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>51 (9.2)</td>
<td>38 (13.2)</td>
<td>13 (4.9)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>2 (0.4)</td>
<td>1 (0.3)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>McNemar chi-squared test</td>
<td>*&lt; 0.01</td>
<td>*&lt; 0.01</td>
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* McNemar chi-squared test.
Incomplete urine collections or inaccurate time recordings by the patients and nurses may have occurred in this study. The timing of the serum creatinine value can influence the 24-hour CCr calculation, and diurnal variation in the serum creatinine level has been reported. To minimize this influence, all serum creatinine measurements were obtained in the morning.

In summary, measured CCr is still useful for NSCLC patients receiving cisplatin-based chemotherapy. The Cockcroft-Gault formula underestimated measured CCr by about 25 mL/min in this series. Cisplatin-based chemotherapy reduced the value of CCr, but without significant difference between older and younger patients. The estimated method would cause significant under-dosing, especially in patients ≥ 65 years old.

References