Retrospective analysis of the carboplatin dosage and relationship with toxicity in cancer patients

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INTRODUCTION

Carboplatin is a 2nd generation platinum by-product, which has been shown to treat a wide range of cancerous...
processes. It is less nephrotoxic, neurotoxic and emetogenic than cisplatin. The main carboplatin dose-limiting toxicity is thrombocytopenia, which is linked with the area under the curve (AUC).

Carboplatin is one of the antineoplastic agents in which the dose has to be adjusted individually according to the estimated clearance and AUC, rather than the dosage method based on body surface area. The Calvert equation is the most commonly used formula for calculating carboplatin dosage:

\[ \text{Dose (mg)} = \text{AUC (mg ml}^{-1} \text{ min)} \times \left( \frac{\text{GFR (ml min}^{-1})}{25} \right) \]

The glomerular filtration rate (GFR) may be measured by the clearance of radioisotopes such as \(^{51}\text{Cr-EDTA}\) or \([\text{Tc}^{99m}]\) DTPA. However, such methods are expensive and are not used in daily practice. There is no consensus on how to determine GFR without using radioisotopes. Many authors have therefore estimated GFR by determining creatinine clearance (Cl Cr) using different formulas: Cockcroft-Gault, Jellife, Jellife corrected for body surface area and Wright. In addition, Chatelut put forward another formula, which estimates carboplatin clearance directly using the concentration of serum creatinine (SCr), along with patient weight, sex, and age.

The Cockcroft-Gault formula is the most commonly used in clinical practice to calculate GFR. This equation includes two variables (weight and SCr), which depend on the patient’s body composition. As a result, when using the Cockcroft-Gault formula, overweight or cachectic patients’ low SCr values are most at risk of receiving incorrect doses of carboplatin.

In the case of cachectic patients, it is possible that low SCr values may not really reflect their actual Cl Cr, and they are therefore at risk of receiving overdoses of carboplatin if the said SCr values are used in the Cockcroft-Gault formula. To avoid this, the SCr value is often rounded up to a prefixed one and then incorporated into the Cockcroft-Gault equation. Dooley et al. validated a method for adjusting SCr values in patients with SCr levels which were lower than 0.67 mg/dl. This was done by comparing the GFR, measured by the \([\text{Tc}^{99m}]\) DTPA, with the estimated ClCr in the aforementioned patients, when the SCr levels were adjusted to 0.67 mg/dl. They concluded that when SCr values were rounded up to the aforementioned value, the estimated Cl Cr was close to the actual GFR, when this was \(\leq 100\) ml/min.

Herrington et al. have put forward the most suitable formula for carboplatin dosage in cachectic and overweight/obese patients. For this purpose, patients were stratified into 2 cohorts according to body mass index (BMI) and SCr values, as well as other parameters. The cohort of cachectic patients included those with BMI < 27 and a SCr value of < 0.8 mg/dl. The cohort of overweight/obese patients included those with BMI \(\geq 27\) and a SCr value of \(\geq 0.7\) mg/dl. The results obtained showed that for the cohort of obese patients, the use of adjusted weight in the Cockcroft-Gault formula produced more accurate carboplatin dosages than the use of total weight for these patients. For the cachectic patients with low SCr values, the use of a SCr value which was adjusted to 0.8 mg/dl produced more accurate results and less bias than the use of the patients’ SCr value or the Chatelut equation.

Therefore, according to the two studies above, the carboplatin dose should be calculated taking into account the BMI and SCr value, since ignoring these data, which are directly included in the Cockcroft-Gault equation, could lead to overdoses of the drug.

Given that carboplatin toxicity is dose dependent, overdosing may produce adverse effects such as thrombocytopenia, which may result in dose reduction in subsequent cycles.

The main objective of this study was to perform a retrospective analysis of carboplatin dosage in cancer patients during their first cycle of chemotherapy, in order to establish whether they were over or underdosed compared to the estimated theoretical dose, taking into account the patients’ BMI and SCr value. The secondary objective was to establish whether there was a link between dosage and dose reduction in subsequent cycles, as a result of adverse effects related to the same.

**METHOD**

A retrospective analysis was performed on chemotherapy prescriptions between December 2004 and November 2005 to select patients in our hospital who were treated with different chemotherapy regimes which included carboplatin. The IT application Oncofarm v. 4.0, for managing cancer patients, was used. The following data were obtained on the first day of the chemotherapy cycle: anthropometric data (weight, size, body surface area), demographic data (sex, age), chemotherapy regime, diagnosis, number of cycles received and analytical data (serum creatinine calculated using the enzymatic kinetic method, creatinine clearance), as well as the dose of carboplatin prescribed during the first cycle of chemotherapy and the AUC used to calculate this. In the case of patients who had their dose of carboplatin reduced in subsequent cycles as a result of negative side effects, the dose and cycle number in which the dose was reduced was also recorded.

The literature relating to clinical trials with carboplatin published in Medline/Pubmed between 1992 and 2006 was reviewed in order to obtain the theoretical AUCs based on chemotherapy regime and diagnosis, and in this way calculate the theoretical dose for each patient. In cases where various AUC values could be used for the same chemotherapy regime and diagnosis, the mean of these values was obtained. The carboplatin AUCs described in the literature according to chemotherapy regime are outlined in table I.
A comparison was drawn between the MPE value and dose reduction in subsequent cycles for each patient belonging to the groups in which the difference between the actual and theoretical dose was statistically significant. The MPE value was categorised in such a way that when the MPE was > 0, this variable took the “over-dosed” value and when the MPE was ≤ 0, it took the “non-over-dosed” value. The percentage by which the dose was reduced was calculated as the percentage of the difference between the initial dose and the dose received in subsequent cycles, in comparison to the initial dose.

The Kolmogorov-Smirnov test was initially used to study the existence of a link between the patients’ initial state of overdosing and the consequent dose reduction. According to the result obtained, a T-test was then used for independent samples (groups with normal distribution) or the Mann-Whitney U test (groups with abnormal distribution). The SPSS® v.10.0 program was used.

### RESULTS

A total of 102 patients undergoing treatment with carboplatin during the study period were selected. Sixteen of these did not comply with the inclusion criteria (5 patients had insufficient anthropometric data on day 1 of the first cycle of chemotherapy to facilitate the BMI to be calculated, and there were 11 patients with BMI ≥ 27 and a SCr value of < 0.7 mg/dl). The distribution of patients per group is shown in table II.

For each group of patients the theoretical dose that they should have received was calculated as follows: for group I the Cockcroft-Gault formula with adjusted weight was used; for groups II and IV the Cockcroft-Gault equation with actual weight was used; for group III the Cockcroft-Gault equation with actual weight and SCr value adjusted to 0.8 mg/dl was used. The Clavert equation was used to obtain the theoretical dose, however, GFR was substituted by the CLcr values obtained.

The theoretical dose calculation and actual dose received during the first cycle were compared for each patient using the mean percent error (MPE). A positive value indicates overdosing and a negative value indicates underdosing.

\[
MPE = \left( \frac{\text{Actual dose} - \text{Theoretical dose}}{\text{Theoretical dose}} \right) \times 100
\]

For each group of patients, the mean MPE value with its standard error (SE) and 95% confidence interval (95% CI) was calculated.
were overdosed, with a mean percentage of 15.24% for the total dose reduction. The results of the aforementioned test are shown in Table V. The differences found in dose reduction between both subgroups were not statistically significant.

**DISCUSSION**

As in a recent published article \( ^{9} \), the results of the present study show that overweight/obese patients are overdosed by approximately 8%. This may be due to the fact that the adjusted weight was not used in the Cockcroft-Gault equation to obtain creatinine clearance. According to studies by Herrington et al. \( ^{2} \) and Dooley et al. \( ^{2} \), overweight and cachectic patients are at most risk of overdosing with carboplatin. The present study was not able to demonstrate theoretical overdosing in patients included in the cachectic group. This may be due to the small number of patients in this group (group III: 14; group IV: 5) and because the cachectic patients in this study did not strictly comply with all the inclusion criteria described by Herrington. In addition to BMI < 27 and an SCr value of < 0.8 mg/dl, these patients also had to have albumin concentration levels lower than 34 g/l and experienced weight loss higher or equal to 15% in the last 6 months. These last two criteria were not recorded in the clinical histories. Another point to be borne in mind, and which may have caused the magnitude of the MPE in patients to vary, is the fact that the carboplatin dose calculated in the first cycle may have been rounded up, or that the dose may have been adjusted to the vials sold or based on the patient’s condition. Since this was a retrospective study it was not possible to control these two aspects.

Patients who did not comply with the inclusion criteria based on BMI and SCr values could be included in another study. Herrington et al. adjusted the SCr value to a prefixed one in adult patients with BMI ≥ 27 and a SCr value of < 0.7 mg/dl. However, they did not show that this adjustment results in correct doses of carboplatin. This group of patients was therefore not included in the present study.

In the present study for overweight/obese patients, no link was shown between overdosing of carboplatin during the first cycle and dose reduction in subsequent cycles, despite this being described in the literature \( ^{27} \). It is to be noted that of the 35 overweight/obese patients who received more than one cycle with carboplatin, the

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**Table III. Results for mean MPE group**

<table>
<thead>
<tr>
<th>Group</th>
<th>MPE ± SE (%)</th>
<th>IC 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>7.963 ± 2.610</td>
<td>2.685 to 13.241</td>
</tr>
<tr>
<td>Group II</td>
<td>3.896 ± 3.406</td>
<td>-3.119 to 10.911</td>
</tr>
<tr>
<td>Group III</td>
<td>6.779 ± 3.830</td>
<td>-1.496 to 15.053</td>
</tr>
<tr>
<td>Group IV</td>
<td>-6.120 ± 3.945</td>
<td>-17.072 to 4.832</td>
</tr>
</tbody>
</table>

MPE: mean percent error; SE: standard error; (95%) CI: confidence interval.

**Table IV. Results of Kolmogorov-Smirnov test for the normality hypothesis of the samples**

<table>
<thead>
<tr>
<th>n</th>
<th>Dose reduction in overdose patients</th>
<th>Dose reduction in non-overdosed patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>-</td>
<td>10</td>
</tr>
</tbody>
</table>

Normal parameters \( ^{**} \)

- Mean: 4.2176; 7.7640
- Standard deviation: 7.2778; 11.2791
- More extreme differences
  - Absolute: 0.399; 0.354
  - Positive: 0.399; 0.354
  - Negative: -0.281; -0.246

Z of Kolmogorov-Smirnov

- 1.994; 1.121

Asintotic significance (bilateral)

- 0.001; 0.162

\( ^{*} \): the contrast distribution is normal; \( ^{**} \): calculated bases on the data.

**Table V. Results of Mann-Whitney U test**

<table>
<thead>
<tr>
<th>Reducion of carboplatin dose</th>
<th>Mann-Whitney U</th>
<th>W of Wilcoxon</th>
<th>Z</th>
<th>Asintotic significance (bilateral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann-Whitney U</td>
<td>109</td>
<td>434</td>
<td>-0.690</td>
<td>0.490</td>
</tr>
</tbody>
</table>

\( ^{*} \): Grouped by their initial dosage variable: overdosed vs. non-overdosed.
dose was subsequently reduced for 12 of them and that the dose was only reduced once for these 12 patients. There were more patients who had their dose reduced in the overdosed than in the non-overdosed subgroup (8 and 4 respectively); however, the dose reduction was quantitatively higher in the non-overdosed than in the overdosed subgroup (19.41 vs. 13.18%).

At all times it was considered that the carboplatin dose reduction was due to its dose dependent toxicity. However, in practice it is not uncommon that toxicity leads not to a dose reduction rather a change in the treatment protocol. This eventuality was not taken into account in the present study and it may have been the reason why 6 of the patients in group I only received one cycle.

References

15. Markman M, Glass T, Smith HO, Hatch KD, Weiss GR, Taylor SA, et al. Phase II trial of single agent carboplatin followed by dose-inten-