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Carboplatin dosing: the importance of creatinine

Abstract

Objective: Compare the dose received with the estimated theoretical dose, considering the body mass index and serum creatinine concentration of each patient.

Method: Observational, retrospective, descriptive study on carboplatin dosing based on the estimation of renal function and the area under the target curve in 74 patients treated with cycles of chemotherapy that included carboplatin in the oncohematology day hospital.

Results: The analysis revealed that in 72% of the patients, the creatinine values used to calculate the dose were higher than the actual values, resulting in under-dosing in most patients.

When comparing the estimated theoretical dose and the administered dose, an intraclass correlation coefficient (ICC) of 0.929 (95% CI: 0.774 - 0.970) was obtained in normal weight patients and 0.819 (95% CI: 0.353 - 0.930) in overweight or obese patients. It was observed that the discrepancy between theoretical and prescribed doses increased with increasing theoretical dose of carboplatin.

Conclusions: The findings of this study underscore the importance of using actual serum creatinine values in the calculation of carboplatin dose as a key measure to minimize under--dosing in carboplatin administration.

Keywords: carboplatin, serum creatinine, body mass index, calvert

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Abbreviations: GFR, glomerular filtration rate; AUC, area under the curve; CG, Cockcroft-Gault; Crs, serum creatinine; BMI, body mass index; FDA, food and drug administration; NCCN, national comprehensive cancer network; CrCl: creatinine clearance; ICC, intraclass correlation coefficient

Introduction

Carboplatin is an antineoplastic agent that is excreted mainly by the renal route, so the dose should be adjusted according to renal function (glomerular filtration rate (GFR)) and the area under the target concentration-time curve (AUC) using Calvert formula[1,2]:

Dose (mg) = AUC (mg x min/mL) x [GFR (ml/min) + 25 (ml/min)]

GFR is estimated using different formulas:[3] Cockcroft-Gault (CG) (using current weight, ideal weight or adjusted weight), Jellife and Jellife corrected with body surface area (Table 1)[4].

Table 1 Description of glomerular filtration rate formulas

GFR Equation name	GFR formule
Jelliffe	Male: CrCl (ml/min) = (98 - (0.8 * (age - 20)) / (Crs in mg/dL)) Female: multiply the above result by 0.9
Jelliffe (adjusted for body surface area)	Male: CrCl (ml/min) = (98 - (0.8 * (age - 20)) / (Crs in mg/dL)) x patient's ASC/1.73 M2 Female: multiply the previous result by 0.9
CG (using current weight)	Male: CrCl (ml/min) = (140 - age) x current weight (kg) / (Crs x 72) Female: multiply the above result by 0.85
CG (using ideal weight)	Male: CrCl (ml/min) = (140 - age) x ideal weight (kg) / (Crs x 72) Female: multiply the above result by 0.85
CG (using adjusted weight)	Male: CrCl (ml/min) = (140 - age) x adjusted weight (kg) / (Crs x 72) Female: multiply the above result by 0.85

GFR: glomerular filtration rate; CG: Cockcroft-Gault; CrCl: creatinine clearance; Crs: serum creatinine.

One of the most used formulas is the CG formula[5]. In it, two variables appear (weight and serum creatinine (Crs)) that depend on the patient's body composition; therefore, overweight or cachectic patients with low Crs values are those most at risk of suffering inappropriate dosing if we use this formula. In contrast, the Jellife formula only takes into consideration Crs.[5–8] Clinical guidelines recommend using CG with current weight for normal-weight patients and CG with adjusted weight in overweight/obese (Body Mass Index (BMI) ≥ 25 kg/m²)[9,10] to calculate the carboplatin dose.

Regarding the Crs value, the Food and Drug Administration (FDA), in 2010, published an alert on carboplatin dosing based on Crs. It points out that low Crs values could lead to the calculation of higher than desired carboplatin doses and lead to the appearance of toxicity.[11] It therefore establishes a maximum dose of carboplatin using the Calvert formula where the GFR should not exceed 125 ml/min (Table 2)[12].

Table 2 Maximum dose according to AUC

AUC	Maximum dose
6	900 mg
5	750 mg
4	600 mg

AUC: Area under the Curve

In line with the alert issued by the FDA, the latest National Comprehensive Cancer Network (NCCN) guidelines, updated in 2023, point out that low Crs values (< 0.7 mg/dl) may not actually reflect the true creatinine clearance (ClCr), so patients are at risk of receiving carboplatin overdoses if such Crs are used. To avoid this, the NCCN guidelines recommend using a minimum Crs of 0.7 mg/dl in case the patient's actual Crs is < 0.7 mg/dl.[10]

In carboplatin dosing, it is essential to consider both the patient's weight, supported by an extensive literature describing the most appropriate formulas for its calculation based on BMI, as well as the Crs. Following the FDA alert, Crs has gained relevance in dose calculation, however, studies evaluating its impact on optimal dosing remain limited.

Although a minimum Crs value or maximum glomerular filtration rate value used to avoid overdoses of carboplatin and its associated toxicity is well established, there is not as much evidence on the potential underdosing that can occur with the use of creatinine values higher than the real values in the calculation of carboplatin doses.

The aim of the study is to compare the dose of carboplatin that is prescribed and received by oncology patients in our center with respect to the estimated theoretical dose, considering the variables of BMI and real Crs of each patient.

Material and methods

An observational, retrospective, descriptive study was conducted to analyze carboplatin dosing based on renal function and desired AUC in patients over 18 years of age who received a dose of carboplatin. Patients with dose reduction due to toxicity or participating in clinical trials were excluded. The enrollment and data collection period spanned four weeks. The study was approved by the hospital's Research and Drug Evaluation Committee.

Data were obtained from the prescribing program and electronic medical records. Variables collected included sex, age, Crs, weight, height, body surface area, target AUC and carboplatin dose. For the calculation of the GFR with the different formulas: CK and Jeliffe (Table 1), we used the web calculator: https://globalrph.com/medcalcs/carboplatin-auc-calculator/[13]

For dose calculation, two methods were used:

I. The electronic prescribing software, parameterized to calculate carboplatin dose using the Calvert formula and the CG formula for GFR with ideal weight. The prescriber manually entered the desired carboplatin AUC, weight, height and Crs of the patient into the software. The parameterized program, with all the data, automatically calculated the individualized dose for each patient, called the actual dose.

II. External dose calculations using the Calvert formula and different GFR equations (Jellife, Jellife adjusted for body surface area, and CG using ideal, current, and adjusted weight). These calculations were performed with an online calculator https://globalrph.com/medcalcs/carboplatin-auc-calculator/[13]. The investigators entered the desired carboplatin AUC and patient data extracted directly from their medical records. The AUC used was the one indicated by the physician for that patient according to his pathology. If Crs was < 0.7 mg/dL, a minimum value of 0.7 mg/dL was used according to FDA guidelines[10], resulting in the estimated theoretical dose.

Patients were divided into two subgroups according to their BMI: normal-weight (BMI <25) and overweight/obese (BMI ≥25).

All extracted data were analyzed using Stata statistical software version 18 (StataCorp. 2023. *Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.).*

We assessed whether the estimated theoretical dose matched the actual dose prescribed and administered to patients receiving a course of carboplatin. The statistical analysis was based on the estimation by two-way mixed-effects model of the intraclass correlation coefficient (ICC), where 0 indicates no concordance and 1 indicates concordance or absolute reliability of the results obtained. The corresponding 95% confidence intervals were also estimated.

In addition, the nonparametric Wilcoxon paired-ranks test was performed to determine whether there were statistically significant differences between the patients' actual Crs levels extracted from their medical records and those entered by the physician in the electronic prescription program.

Results

A total of 74 patients on carboplatin treatment (55.4% women) were included, with a mean age of 63.25 years (range 37 to 85 years). In relation to BMI, 51% of the patients had a BMI < 25, while 49% had a BMI > 25. Within the latter group, 72% were overweight and 28% obese. The diagnoses of these patients were non-small cell lung cancer (31.10%), ovarian cancer (16.21%) and breast cancer (13.51%).

In 28% of the patients, the actual Crs value was the value entered for the cycle dose calculation. In 72% of the remaining patients, the actual value was lower than the value entered in the electronic prescription program. These data were analyzed with the Wilcoxon test and significant differences were detected between the actual Crs levels and the Crs used in the electronic prescription program, with a p value < 0.001 (Table 3).

Table 3 Distribution of Real vs. Applied creatinine values in trial population

	Frequency	Percent
No	53	71.62
Yes	21	28.37
Total	74	100

Variable	N	Mean	SD	p50	p25	p75
Applied Crs	74	0.97	0.24	1	0.8	1.1
Real Crs	74	0.85	0.26	0.78	0.66	1.02
Crs difference	74	0.12	0.15	0.1	0	0.18

Cr: serum creatinine.

Wilcoxon signed-rank test: Prob > |z| = 0.0000

When measuring the concordance between the theoretical dose and the actual dose received, in the normal-weight subgroup (38 patients) an ICC of 0.929 (95% CI: 0.774 - 0.970). As shown in the Bland-Altman plot (Figure 1), these patients received on average 45 mg (6.96%) less carboplatin than the theoretical dose. The difference

between theoretical dose and prescribed dose administered increased as the theoretical dose was higher.

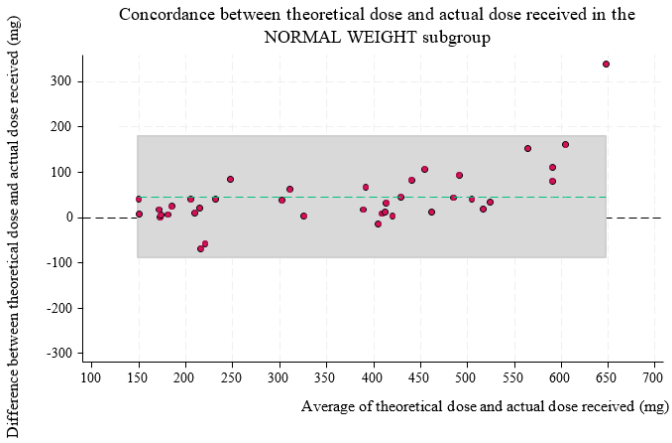

Figure 1 Bland-Altman graph.

In the subgroup of overweight/obese patients (36 patients), the ICC was 0.819 (95% CI: 0.353 - 0.930), showing a greater difference compared to the group of normal-weight patients. Patients in this subgroup received an average difference of 128 mg (9.78%) less than the theoretical dose. As in the normal-weight subgroup, the discrepancy between the theoretical and administered dose increased with higher theoretical doses (Figure 2).

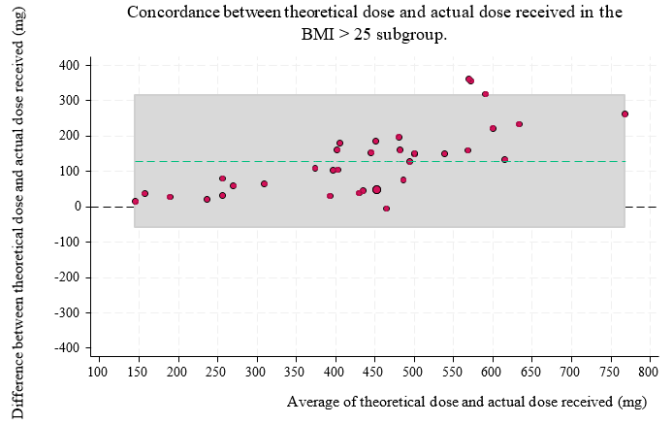

Figure 2 Bland-Altman graph.

Discussion

The study was prompted by the variability in the calculation of carboplatin doses between hospitals, as evidenced in a 2019 survey of 186 hospital pharmacies in Spain. The results highlighted the need to investigate an optimal calculation method and unify criteria to improve efficacy and reduce toxicity.[14]

Accurate estimation of GFR based on creatinine levels is essential for individualizing carboplatin dosing, as the drug's pharmacokinetics, and consequently its therapeutic efficacy and toxicity, are highly influenced by renal function.[15,16]

To evaluate our calculation method, we compared the theoretical doses with patient´s doses received, finding significant differences between the two. A high percentage of patients, in both subgroups, received doses lower than those recommended according to calculations based on their clinical parameters extracted from the medical history. This is attributed to the fact that, in 72% of the cases, the actual Crs value was lower than the value used to prescribe the carboplatin dose, resulting in a lower administered dose. This practice is common among prescribing physicians, who adopt a cautious approach with the aim of minimizing the risk of adverse effects and toxicity in patients.

Likewise, it is evident that the differences are more notable in the overweight/obese group, as reflected by the ICC. Our study is in line with the study by García-Palomo et al.,[14] where they found differences between the actual and administered doses of carboplatin as a function of the creatinine values used and the patients' weights, these being significant in the overweight group, also concluding that the non-use of the patient's actual Crs can result in inappropriate dosing of carboplatin in patients with obesity.[14]

The measurement of Crs routinely performed in clinical practice has several limitations in interpreting renal function as it is affected by muscle mass, gender, diet and renal tubular secretions.[17]

Despite concerns related to carboplatin underdosing, our results do not allow us to demonstrate that this possible underdosing is associated with a decrease in the efficacy of chemotherapeutic treatment. This finding highlights the need for further studies to confirm its clinical relevance.

The main limitations of our study are its retrospective and single-center nature, together with the limited number of patients and the manual entry of Crs values in the electronic prescription program.

Conclusion

Based on our study, we conclude that using Crs values higher than the real value in patients leads to underdosing, with the degree of underdosing being more pronounced in overweight or obese patients.

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None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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References

1. Arbesú Michelena MA, Proveyer Derich S, Ropero Toirac R. Detection of potential prescription errors of carboplatin by pharmaceutical validation. *Revista Cubana de Farmacia*. 2011;45(2):244–250.
2. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol*. 1989;7(11):1748–1756.
3. Nagao S, Fujiwara K, Imafuku N, et al. Difference of carboplatin clearance estimated by the Cockcroft- Gault, Jellife, Modified-Jellife, Wright or Chatelut formula. *Gynecol Oncol*. 2005;99(2):327–333.
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41.
5. De Jonge ME, Mathot RA, Van Dam SM, et al. Extremely high exposures in an obese patient receiving high-dose cyclophosphamide, thiotepa and carboplatin. *Cancer Chemother Pharmacol*. 2002;50(3):251–255.
6. Dooley MJ, Singh S, Rischin D. Rounding of low serum creatinine levels and consequent impact on accuracy of bedside estimates of renal function in cancer patients. *Br J Cancer*. 2004;90(5):991–995.

7. Herrington JD, Tran HT, Riggs MW. Prospective evaluation of car- boplatin AUC dosing in patients with a BMI > or = 27 or cachexia. *Cancer Chemother Pharmacol*. 2006;57(2):241–247.

8. Kicken M, Kilinc H, Cramer-van der Welle C, et al. The association of Body Mass Index on safety and effectiveness of first-line carboplatin-based chemotherapy in patients with metastatic non-small cell lung cancer. *Cancer Treat Res Commun*. 2023;34:100676.

9. Nccn.org.

10. Percy Ivy S, Zwiebel J, Mooney M. *Follow up for information letter regarding AUC-based dosing of carboplatin*. Department of Health and Human Services (FDA). 2010.

11. Morrow A, Garland C, Yang F, et al. Analysis of carboplatin dosing in patients with a glomerular filtration rate greater than 125 mL/min: To cap or not to cap? A retrospective analysis and review. *J Oncol Pharm Prac.* 2019;25(7):1651–1657.

12. Cuesta-Grueso C, Burgos-San José A, Cajaraville-Ordoñana G, et al. Variability of carboplatin dose calculation methods in Spain. *J Oncol Pharm Pract*. 2019;25(7):1551–1557.

13. Carboplatin AUC Calculator. GlobalRPH.

14. García Palomo M, Castellanos Clemente Y, Díez Fernández R, et al. Retrospective analysis of the carboplatin dosage and relationship with toxicity in cancer patients. *Farm Hosp.* 2007;31(4):218–222.

15. Chatelut E, Canal P, Brunner V, et al. Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J Natl Cancer Inst*. 1995;87(8):573–580.

16. White-Koning M, Paludetto M, Louedec F, et al. Formulae recently proposed to estimate renal glomerular filtration rate improve the prediction of carboplatin clearance. *Cancer Chemother Pharmacol.* 2020;85(3):585–592.

17. Thomas D, Zachariah S, Elamin AEE. Limitations of serum creatinine as a marker of renal function. *Sch Acad J Pharm.* 2017;6(5):168–170.

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