Optimizing carboplatin dosing using Computed Tomography derived body composition and serum creatinine

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The overall objective of this study is to develop and evaluate an optimized dosing algorithm (CT-CL) for carboplatin using serum creatinine and CT-derived body composition that can be easily implemented in clinical practice.

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Observational invasive

Summary

ID

NL-OMON56726

Source
ToetsingOnline

Brief title
POPCORN study

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Lung cancer, ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: Amphia Ziekenhuis
Source(s) of monetary or material Support: Met geld vanuit het Amphia wetenschapsfonds en Catharina onderzoeksfonds.

Intervention

Keyword: Carboplatin, creatinin, CT-scan, Dose optimalisation

Outcome measures

Primary outcome

The covariate relationship between CT-derived body composition, serum

creatinine, and carboplatin pharmacokinetics.

Secondary outcome

o The bias (Mean Percentage Error, MPE%), the imprecision (Mean Absolute

Percentage Error, MAPE%) and the accuracy (Root Mean Squared Error, RMSE) of

the predicted AUC versus the target AUC

o The percentage of patients within 90-110% the target AUC will be assessed

Study description

Background summary

Carboplatin is an anticancer drug used for the treatment of various types of cancer including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), ovarian cancer, and breast cancer. It is mostly secreted by the kidney with its clearance being linearly correlated with the glomerular filtration rate (GFR). Therefore, the dosing of carboplatin is based on the GFR, and the target exposure is expressed as the target Area Under the Curve (AUC) using the Calvert formula. In clinical practice, the GFR is substituted by the estimated creatinine clearance (CrCl) using the Cockcroft-Gault (CG) formula. CrCL is determined by the difference between creatinine production (i.e. muscle mass) and serum creatinine concentration. The CG formula uses surrogate markers of muscle mass (i.e. age, gender, weight) and serum creatinine to estimate CrCl. However, the CG formula is not well suited for extreme body compositions, often seen in cancer patients, and leads to overprediction in overweight and obese patients or cachectic patients with low serum creatinine values. This can lead to increased risk of (serious) side effects and hospitalization, decreased quality of life, postponement of treatment, and dose reduction. On the other hand, can the CG formula lead to underprediction in underweight patients resulting in potentially inadequate treatment.

A better, specific, and more direct way to measure a patient's muscle mass can be done using a CT-scan already performed in standard-of-care. Recent advances in deep learning and medical imaging have made it possible to utilize regular CT-scans of the skeletal muscle cross-sectional area of lumbar 3 to predict the total muscle mass of a patient accurately. This makes it possible to measure creatinine clearance directly using CT-scans and to predict carboplatin clearance. Subsequently, by estimating carboplatin clearance, a more precise carboplatin dosing can be established, preventing potentially under- or overdosing of carboplatin, especially in patients with extreme body composition.

Study objective

The overall objective of this study is to develop and evaluate an optimized dosing algorithm (CT-CL) for carboplatin using serum creatinine and CT-derived body composition that can be easily implemented in clinical practice.

Study design

This study consists of two parts:
1. PART A is a prospective observational pharmacokinetic study to asses carboplatin pharmacokinetics in relation to CT-derived body composition and serum creatinine and subsequently develop an optimized dosing algorithm.
2. PART B is a simulation study to evaluate the developed dosing algorithm.

Patients are treated for their cancer according to routine clinical practice, standard protocols, and treatment regimens. The dose of carboplatin to be administered will be calculated using the Calvert formula. In addition, a CT-scan including L3 serum creatinine at baseline is used to assess the body composition - both are collected as standard-of-care. Both the abdominal and the thoracal CT-scan include L3. For each patient, five blood samples will be taken on day 1 of the first cycle of carboplatin treatment.

Next, a virtual cohort of 1000 patients will be simulated with NONMEM V7.4 using Monte Carlo simulations. This population will be generated using the virtual human population generator PopGen (36). For the simulation of the covariates, the median plus distribution found in the study population from the PK analysis will be used. Patients will subsequently be dosed according to the Calvert formula and CT-CL. The simulated AUC will be evaluated on the bias (MPE%), precision (MAPE%), and accuracy (RMSE) relative to the target AUC. Lastly, the percentage of patients within 90-110% of the target AUC (± 10%) will be assessed.

Study burden and risks

All patients will be treated according to standard protocols and treatment regimens. We consider the extra burden of participating in this study limited. The extra interventions, compared to routine care, consist of blood sampling. To ensure the minimal impact of study participation on daily life, we will use a limited sampling strategy of only five blood samples. For each patient five PK samples will be taken on day 1 of cycle 1 of carboplatin treatment for a total of 25 mL. This is a minimal amount compared to the total blood volume of a patient. There is a minimal risk that the venflon may cause slight irritation or thrombophlebitis. All other visits, CT-scan at baseline, and laboratory investigations are performed in standard-of-care.

The aim of this study is to develop and evaluate an optimized dosing algorithm for carboplatin using serum creatinine and CT-derived body composition. The results of this study can improve future treatment of patients with carboplatin, especially with abnormal body composition.

The results of our study can improve future treatment of patients with carboplatin, especially with abnormal body composition, and will help switch from one-size-fits-all formulas to more personalized medicine.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age 18 years or older
- Available contrast-enhanced enhanced CT-scan including L3 at baseline before carboplatin treatment (at least of six weeks before start of therapy)

Exclusion criteria

- Conditions that affect hemostasis in a way that blood drawing is complicated (to be assessed by a physician)
- Drugs that inhibit creatinine clearance in the kidneys, like cimetidine, trimethoprim, pyrimethamine, and salicylates (>100 mg)
- A carboplatin target AUC of below 4 mg/mL*min

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2024
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	28-03-2024
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL86291.028.24