PHARMACOKINETICS OF CARBOPLATIN AFTER ADJUSTED DOSING FOR HIGH BMI, LOW SERUM CREATININE, AND MAXIMAL RENAL FUNCTION

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

Summary

ID

NL-OMON44328

Source
ToetsingOnline

Brief title
Prospective validation of an alternative dosing algorithm of carboplatin

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
lung cancer, ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: ziekenhuisapotheek

Source(s) of monetary or material Support: Subsidie van Rijnstate Vriendenfonds

Intervention

Keyword: cachexia, carboplatin, obesity, pharmacokinetics

Outcome measures

Primary outcome

The primary endpoint is the mean prediction error and the mean absolute prediction error in obtaining the target AUC of carboplatin using the new dosing algorithm.

Secondary outcome

Secondary endpoints are additional pharmacokinetic parameters (including clearance, half life,) of carboplatin using the new dosing algorithm, the relationships between the clearance of carboplatin and the serum cystatine C value and the 24-hour urinary clearance, and safety of treatment defined as treatment-related toxicity, toxicity-related hospitalization and toxicity-related dose adjustments

Study description

Background summary

Carboplatin is an alkylating anticancer drug that is used for the treatment of various types of cancer, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), malignant mesothelioma, ovarian cancer, and breast cancer.
Carboplatin is excreted for approximately 75% in the urine as unchanged drug within 24 hours after administration, and its clearance is proportional to the glomerular filtration rate (GFR). Since carboplatin is highly eliminated by the kidneys, the dose needs to be adjusted for renal dysfunction. There are several formulas that can be used to calculate the individual dose of carboplatin. The Calvert formula [dose = target AUC x (GFR + 25)] is internationally the most

widely used. Herein, the GFR is generally calculated as the estimated creatinine clearance (CrCl), as calculated by the Cockcroft-Gault formula (GFR = CrCl = [140 - age] x weight x 0.85 [if female] / 0.815 / serum creatinine). The Cockcroft-Gault formula is very well suitable to calculate the CrCl in patients with normal weight, and in patients with serum creatinine values above the lower limit of normal (~60 µmol/L). However, in both obese patients and patients with low serum creatinine values, the Cockcroft-Gault equation gives an overestimation of the CrCl. Consequently, using an overestimated CrCl value in the Calvert equation, results in a potential serious overdose of carboplatin, with increased risk for toxicity.
To overcome this problem, we have developed a new dosing algorithm for the dosing of carboplatin which is based on the latest evidence and available guidelines. This dosing algorithm uses:
1] the adjusted ideal body weight instead of actual weight for patients with BMI >= 25 kg/m2
2] a serum creatinine value of 60 µmol/L in patients with serum creatinine < 60 µmol/L, and
3] maintains a maximal calculated (according to the Cockcroft and Gault formula) renal function of GFR = 125 ml/min

The aim of this study is to prospectively evaluate the pharmacokinetics and safety of carboplatin after adjusted dosing for high BMI (BMI >= 25 kg/m2), low serum creatinine (serum creatinine < 60 µmol/L), and maximal renal function (GFR = 125 ml/min).

Study objective

The primary objective of the study is to determine the mean prediction error (MPE) and mean absolute prediction error (MAPE) of the area under the plasma concentration-time curve (AUC) of carboplatin after adjusted dosing for high BMI (BMI >= 25 kg/m2), low serum creatinine (serum creatinine < 60µm/L), and maximal renal function (GFR = 125 ml/min).

Secondary objectives are:
- to determine the safety of carboplatin after adjusted dosing for high BMI, low serum creatinine, and maximal renal function
- to determine the relationship between the measured creatinine clearance, as measured by collection of a 24-hour urine sample, and the pharmacokinetics of carboplatin after adjusted dosing for high BMI, low serum creatinine, and maximal renal function
- to determine the correlation between the measured 24-hour urinary creatinine clearance and the calculated clearance using the adjusted Cockcroft-Gault formula (adjusted for high BMI, low serum creatinine and maximal renal function)
- to determine the relationship between serum cystatine C and the pharmacokinetics of carboplatin

Study design

This is an prospective, pharmacokinetic, single-centre study.
Eligible patients will be treated for their cancer according to routine clinical practice and standard protocols and treatment regimens. The dose of carboplatin to be administered will be calculated according to the modified Cockcroft-Gault formula, i.e.: in patients with BMI >= 25 kg/m2 the dose will be calculated using the adjusted ideal body weight in stead of actual weight; in patients with serum creatinine of < 60 µmol/L the dose will be calculated using a serum creatinine value of 60 µmol/L instead of actual serum creatinine; and in patients with a calculated GFR of > 125 ml/min, the dose will be calculated maintaining a maximum GFR of 125 ml/min (figure 1).
In 24 patients, on the first day of cycle 1 of treatment, an additional four blood samples will be obtained for pharmacokinetic purposes. Furthermore, these patients will be asked to provide a 24-hour urine sample the day before start of treatment in order to determine the measured creatinine clearance. In addition, safety (i.e. haematological and non-haematological toxicity) of each cycle of treatment will be assessed.

Study burden and risks

All patients will be treated according to standard protocols and treatment regimens. On day 1 of cycle 1 an additional 4 blood samples (8 ml heparinized collection tubes) will be obtained for pharmacokinetic purposes at the end of infusion, and at t = 1 h, 2.5 h and 5 h after the end of the infusion. Furthermore, this blood will be used to determine the cystatine C value. These blood samples will be obtained using a venflon, which requires one extra venous puncture. There is a minimal risk that the venflon may cause slight irritation or thrombophlebitis. Furthermore, these 24 patients will be asked to provide a 24-hour urine sample the day before start of treatment. this sampling takes time for the patient, but is not associated with any risks. All other visits and laboratory investigations are standard care.

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

- any type of histologically or cytologically proven solid tumor for which treatment with carboplatin is indicated
- to be treated with carboplatin with a target AUC of 4, 5 or 6
- age 18 years or older
- WHO status 0 - 2
- adequate bone marrow and liver function defined as
o haemoglobin >= 6.0 mmol/L
o white blood cell count >= 3.0 * 109/L
o absolute neutrophil count (ANC) >= 1.5 * 109/L
o platelets >= 100/L
o bilirubin <= 1.5 times ULN
o ALAT and ASAT <= 2.5 times ULN (in case of liver metastases <= 5.0 times ULN).
- estimated life expectancy of at least 12 weeks

Exclusion criteria

- Treatment with carboplatin with a target AUC of <4
- active clinically serious infection
- history of a kidney allograft
- pregnant
- patients not suitable for follow-up

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-09-2014
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	paraplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-05-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-09-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-02-2016

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2014-000234-33-NL
ClinicalTrials.gov	NCT02103244
CCMO	NL47559.091.14

Study results

Date completed:	31-01-2018
Actual enrolment:	24