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Extremely high exposures in an obese patient receiving high-dose cyclophosphamide, thiotepa and carboplatin

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Abstract An obese 53-year-old woman (height 167 cm, weight 130 kg) with metastatic breast cancer received high-dose chemotherapy comprising cyclophosphamide, thiotepa and carboplatin (CTC). The cyclophosphamide (1 g/m² per day) and thiotepa (80 mg/m² per day) doses were based on body surface area (BSA) calculated using total body weight (TBW). The daily carboplatin dose was calculated based on the Calvert formula, using a target area under the plasma concentration-time curve (AUC) value of 3.25 mg·min/ml and applying the Cockcroft-Gault equation to estimate the glomerular filtration rate. The patient received the three agents as short infusions over four consecutive days. For therapeutic drug monitoring (TDM), blood samples were collected on day 1. Thiotepa and its main metabolite tepa, ultrafilterable platinum, cyclophosphamide and its activated metabolite 4-hydroxycyclophosphamide were determined. Individual pharmacokinetics were assessed using Bayesian analysis. Exposure to the individual compounds was determined by calculating the AUC. Exposures to 4-hydroxycyclophosphamide, the combination of thiotepa/tepa and carboplatin were 94%, 117% and 71% higher than the median respective exposures in a non-obese population of patients (n = 24) receiving similar doses. Because high AUCs of 4-hydroxycyclophosphamide, thiotepa/tepa and carboplatin correlate with increased toxicity, the treatment risk in this obese patient was significantly increased. Therefore doses were adapted on the 3rd day of the course. It is concluded that cyclophosphamide and thiotepa in obese patients should not be dosed on the basis of BSA incorporating TBW since the patient will be overexposed. Moreover, applying the Cockcroft-Gault equation to obese patients leads to an overprediction of creatinine clearance and, when used in the Calvert equation, consequently to a carboplatin dose that is too high. Obese patients represent a unique group of patients in which TDM is extremely valuable in optimizing dosing, particularly in high-dose chemotherapy.

Keywords Obese · Dosage · Cyclophosphamide · Thiotepa · Carboplatin

Introduction

High-dose chemotherapy in combination with peripheral blood progenitor cell transplantation is widely used in the treatment of haematological malignancies and in certain solid tumours. Frequently employed regimens in solid tumours include combinations of cyclophosphamide, thiotepa and carboplatin (CTC) [15, 16, 17, 18]. The “tiny” CTC (tCTC) regimen is used in our hospital in the treatment of patients with stage IV hormone-refractory breast cancer [16]. It is administered as three courses given every 4 weeks. One course of tCTC consists of 4 days of chemotherapy with cyclophosphamide (1000 mg/m² per day) as a 1-h infusion, followed by carboplatin (dosed on the basis of the Calvert formula [4] with 3.25 mg·min/ml as daily target area under the plasma concentration-time curve, AUC) as a 1-h infusion, and thiotepa (80 mg/m² per day) divided into two 30-min infusions.

High-dose chemotherapy can be complicated by the occurrence of severe toxicities. A wide interpatient variability in toxicity of cyclophosphamide, thiotepa and carboplatin has been described, which can be explained in part by the interpatient variability in pharmacokinetics of the respective compounds [9]. Relationships
between the pharmacokinetics and toxicity have been established. Exposure to the prodrug cyclophosphamide appears to be (inversely) correlated with cardiotoxicity [1, 12] and exposure to its cytotoxic metabolite 4-hydroxycyclophosphamide has been correlated with the occurrence of veno-occlusive disease [9]. The AUCs of thiopeta and its metabolite tepa are correlated with elevation of transaminases [9], occurrence of regimen-related toxicity [14] and mucositis [10], while cumulative carboplatin exposure is correlated with the occurrence of ototoxicity [25].

Because cyclophosphamide, thiopeta and carboplatin have low therapeutic ratios and steep dose-effect curves, accurate dosing of these compounds is needed in order to avoid excessive exposures and consequently severe toxicity. To reduce interpatient variability in exposures, anticancer drugs are classically dosed based on body surface area (BSA) in order to “normalize” the drug dose. This dosing method is, however, controversial, especially when applied in obese patients [6, 20]. Similarly, other dosing methods incorporating total body weight (TBW), overestimate dosages in obese patients [22]. Accordingly, oncologists tend to reduce the doses of cytotoxic drugs in obese patients based on the assumption that dosing based on the TBW puts obese patients at a higher risk for toxicity than non-obese patients.

In this report, we describe a markedly obese woman who received tCTC with doses administered calculated using TBW and who subsequently developed very high plasma levels of 4-hydroxycyclophosphamide, tepa and carboplatin. This patient is an example of an obese patient for whom classical initial dose calculations can only be applied with some modifications and for whom therapeutic drug monitoring (TDM) can be valuable.

**Patients and methods**

An obese 53-year-old female (body mass index 47) was enrolled in a clinical study that employed the tCTC high-dose chemotherapy regimen with peripheral blood progenitor cell transplantation as described previously [16]. The patient had advanced breast cancer and, as required for inclusion in the study, normal cardiac, renal, hepatic, haematopoietic and pulmonary functions. The patient had a history of hypertension and hypercholesterolaemia.

The patient's body measurements were as follows: height 167 cm, TBW 130 kg and consequently a BSA of 2.34 m², calculated using the DuBois and DuBois formula [8]:

\[
\text{BSA} = 0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}
\]

The patient received cyclophosphamide 2340 mg daily (1000 mg/m² per day), thiopeta 93 mg twice daily (80 mg/m² per day) and carboplatin 680 mg daily. The carboplatin dose was calculated using the Calvert equation [4]:

\[
\text{Dose(mg)} = \text{Target AUC (mg·min/ml)} \times \text{GFR(ml/min + 25)}
\]

using a target AUC of 3.25 mg·min/ml.

The Cockcroft-Gault equation was used to estimate the creatinine clearance (Ccr) used as an estimate of the glomerular filtration rate (GFR) [7]:

\[
\text{Ccr(ml/min)} = \frac{\left(140 - \text{age(years)}\right) \times \text{weight(kg)} \times 1.23 \times 0.85}{\text{serumcreatinine(µM)}}
\]

Serum creatinine was determined using the (adjusted) Jaffe method (64 µM), resulting in a Ccr of 185 ml/min.

This procedure for determining the doses of the three drugs was specified by the study protocol. Doses were adapted on the 3rd day of the course to prevent severe overexposure. For the pharmacokinetic analyses, blood samples were collected via a double-lumen intravenous catheter inserted in a subclavian vein. Collection took place on the 1st day of the course, prior to the start of the infusions, at 30 min after the start of the cyclophosphamide infusion and at 60 (end of cyclophosphamide infusion), 90, 120 (end of carboplatin infusion), 150 (end of thiopeta infusion), 180, 210, 270, 380 and 660 min. Sampling procedures as well as analytical methods for the determination of plasma concentrations of cyclophosphamide, 4-hydroxycyclophosphamide, carboplatin (free fraction), thiopeta and tepa have been reported previously [9].

Population pharmacokinetic models of carboplatin, thiopeta (and its metabolite tepa) and cyclophosphamide (and its metabolite 4-hydroxycyclophosphamide) were used as described by Huitema et al. [9]. Based on these population pharmacokinetic models, which were obtained using the nonlinear mixed effect modelling program NONMEM (double precision, version V 1.1), AUC values were calculated for all compounds using Bayesian analysis [2].

The AUC was used as a measure of the exposure to the compounds. Exposure to thiopeta is expressed as the combined AUC of thiopeta and its metabolite tepa (a result of oxidative desulphuration of thiopeta by hepatocytes), because both compounds have comparable alkylating activity and can both be involved in the occurrence of toxicity [24]. Cyclophosphamide is a noncytotoxic prodrug and needs 4-hydroxylation by hepatic cytochrome P450 for activation. Exposure to 4-hydroxycyclophosphamide has been reported to be a good marker of the alkylating activity of cyclophosphamide. Exposure to both cyclophosphamide and its metabolite were therefore evaluated [11].

The AUC values of the different compounds in our patient were compared with the respective median AUC values in a non-obese population of patients (n = 24, median weight 69 kg, range 52–90 kg). This reference population also received tCTC and was dosed and sampled as described above. Complete pharmacokinetic profiles of the population were available for day 1 and day 3 or 4.

The patient was participating in a clinical study, which was approved by the Committee on the Medical Ethics of the Netherlands Cancer Institute.

**Results and discussion**

Dosing of cyclophosphamide and thiopeta based on (unadjusted) BSA in this obese patient led to excessive exposures to 4-hydroxycyclophosphamide and tepa. Dosing of carboplatin in this same patient based on the Calvert formula, calculating the GFR using the Cockcroft-Gault equation (incorporating TBW), also resulted in higher carboplatin exposures than obtained in the reference population. Table 1 shows the median cumulative exposures following one course in both the population and the obese patient, the latter based on the pharmacokinetics obtained on the 1st day of the 4-day course. Figure 1 shows how the plasma concentration-time data