Cancer Chemother Pharmacol (2002) 50: 251–255
DOI 10.1007/s00280-002-0494-7

SHORT COMMUNICATION

Milly E. de Jonge · Ron A.A. Mathôt
Selma M. van Dam · Jos H. Beijnen · Sjoerd Rodenhuis

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

Received: 7 May 2002 / Accepted: 24 June 2002 / Published online: 30 July 2002

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/m^2 per day) and thiotepa (80 mg/m^2 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

M.E. de Jonge (✉) · R.A.A. Mathôt · S.M. van Dam
J.H. Beijnen
Department of Pharmacy and Pharmacology,
The Netherlands Cancer Institute/Slotervaart Hospital,
Louwesweg 6, 1066 EC, Amsterdam, The Netherlands
E-mail: apmil@slz.nl
Tel.: +31205124657
Fax: +31205124753

S. Rodenhuis
Department of Medical Oncology,
The Netherlands Cancer Institute,
Plesmanlaan 121, 1066 CX,
Amsterdam, The Netherlands

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/m^2 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/m^2 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 thiotepa 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, thiotepa 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 m^2, calculated using the DuBois and DuBois formula [8]:

$$\mathrm{BSA} = 0.007184 \times \mathrm{weight}^{0.425} \times \mathrm{height}^{0.725}$$

The patient received cyclophosphamide 2340 mg daily (1000 mg/m^2 per day), thiotepa 93 mg twice daily (80 mg/m^2 per day) and carboplatin 680 mg daily. The carboplatin dose was calculated using the Calvert equation [4]:

$$\mathrm{Dose(mg)} = \mathrm{Target\ AUC\ (mg \cdot min/ml)} \times [\mathrm{GFR(ml/min} + 25)]$$

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]:

$$\mathrm{Ccr(ml/min)} = \frac{[140 - \mathrm{age(years)}] \times \mathrm{weight(kg)} \times 1.23}{\mathrm{serumcreatinine}(\mu\mathrm{M})} * 0.85(\text{for female})$$

Serum creatinine was determined using the (adjusted) Jaffé 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 thiotepa 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), thiotepa and tepa have been reported previously [9].

Population pharmacokinetic models of carboplatin, thiotepa (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 thiotepa is expressed as the combined AUC of thiotepa and its metabolite tepa (a result of oxidative desulphuration of thiotepa 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 thiotepa 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

Table 1. Overall exposure (expressed as AUC) to the different compounds and their metabolites during the course if no dose adjustment had been done

Compound	AUC				Deviation (%)
	Units	Obese patient	Population		
			Median	2.5–97.5% range	
Thiotepa and tepa	$\mu M \cdot h$	560	258	135–384	117
Cyclophosphamide	$\mu M \cdot h$	4960	4552	1507–7370	9
4-Hydroxycyclophosphamide	$\mu M \cdot h$	209	108	44–174	94
Carboplatin	mg·min/ml	25.5	14.9	11.1–19.2	71

in the obese patient deviated from those of the reference population. The plots were derived from the concentration-time data obtained on the 1st day of a course.

Obesity is a factor that may complicate drug dosing, because it has been reported to alter the disposition of several drugs [6]. The practice of using dosages based on pharmacokinetic data obtained in normal-weight individuals could result in errors in these patients. The adipose tissue in obese patients has a smaller proportion of water compared to muscle tissue. Consequently, an obese patient has a smaller ratio of body water per kilogram of body mass compared to a patient with ideal body weight (IBW). Many chemotherapeutic agents are moderately or weakly lipophilic and distribute poorly in adipose tissue. Obese patients may therefore receive a relative overdose of these relatively lipid-insoluble drugs when dose is based on actual body weight. Obesity is also associated with alterations in hepatic and renal functions. Usually, drug clearance is identical or increased in obese patients compared with patients with normal weight [6].

Comparing pharmacokinetic parameters of cyclophosphamide, thiotepa and carboplatin in our patient with those in the reference population, it appeared that the total body clearance of cyclophosphamide and thiotepa was moderately increased in the obese patient compared with the population parameters (6.0 vs 5.1 l/h and 43.2 vs 34.5 l/h, respectively). Increased clearance of cyclophosphamide and thiotepa could be due to an increase in oxidative metabolism in the liver, which is an explanation for the high plasma concentrations of the metabolites 4-hydroxycyclophosphamide and tepa. The clearance of carboplatin in the obese patient was slightly decreased (6.41 vs 7.52 l/h).

The apparent volumes of distribution of cyclophosphamide, thiotepa and carboplatin, expressed as litres per kilogram, were lower in the obese patient than in the population (0.38 vs 0.55 l/kg, 0.51 vs 0.66 l/kg and 0.13 vs 0.20 l/kg, respectively). As mentioned above, this is normal for drugs with moderate or weak lipophilicity. The applied population pharmacokinetic models do not allow assessment of the volumes of distribution of the metabolites 4-hydroxycyclophosphamide and tepa. However, another explanation for the extremely high plasma concentrations of these (more hydrophilic) metabolites in the obese patient (Fig. 1) may be that the distribution volumes of tepa and 4-hydroxycyclophosphamide hardly increase with additional fatty tissue.

In this patient, initial cyclophosphamide and thiotepa doses were calculated on the basis of BSA. In medical oncology it is common practice to dose chemotherapeutic agents on the basis of BSA in order to reduce interpatient variability in exposure. However, the use of BSA as a determinant of drug dosing in patients has been criticized because BSA often does not correlate well with drug pharmacokinetic parameters [20].

Powis et al. did not find a correlation between apparent volume of distribution of cyclophosphamide and TBW in a small group of patients including obese patients [13]. Cyclophosphamide clearance, however, seemed to be decreased in the obese patients. To our knowledge, no other studies have been published describing a correlation between BSA and volume of distribution or clearance of cyclophosphamide. The rationale for dosing cyclophosphamide on the basis of BSA, especially in obese patients, is therefore questionable.

For thiotepa, the volume of distribution in a group of patients, including obese patients, has been found to be correlated with BSA calculated using TBW. However, the volume of distribution was better correlated with BSA calculated using IBW or adjusted body weight (ABW) [14]:

$$\mathrm{IBW(kg)} = 0.9 \times [\mathrm{height(cm)} - 152] + 45.5$$

for a female, and

$$\mathrm{ABW(kg)} = \mathrm{IBW} + 0.4 \times [\mathrm{TBW(kg)} - \mathrm{IBW(kg)}]$$

The authors recommend thiotepa dosing in obese patients on the basis of BSA, using ABW in the calculation of BSA [14].

Carboplatin is predominantly excreted via the kidneys. Its clearance appeared to be highly correlated with GFR. Because the GFR differs with each patient irrespective of BSA, it is common practice to dose carboplatin not on the basis of a patient's BSA but in proportion to GFR, using the Calvert equation. The Cockcroft-Gault equation is the most widely used method for rapidly estimating Ccr in clinical practice. However, in some specific patient groups, such as the obese, this equation is biased and inaccurate [22]. Van de Ree et al. evaluated the influence of extreme obesity on the Cockcroft-Gault formula. They stated that, in view of the influence of body weight in the Cockcroft-Gault formula, it should not be used to estimate the GFR in

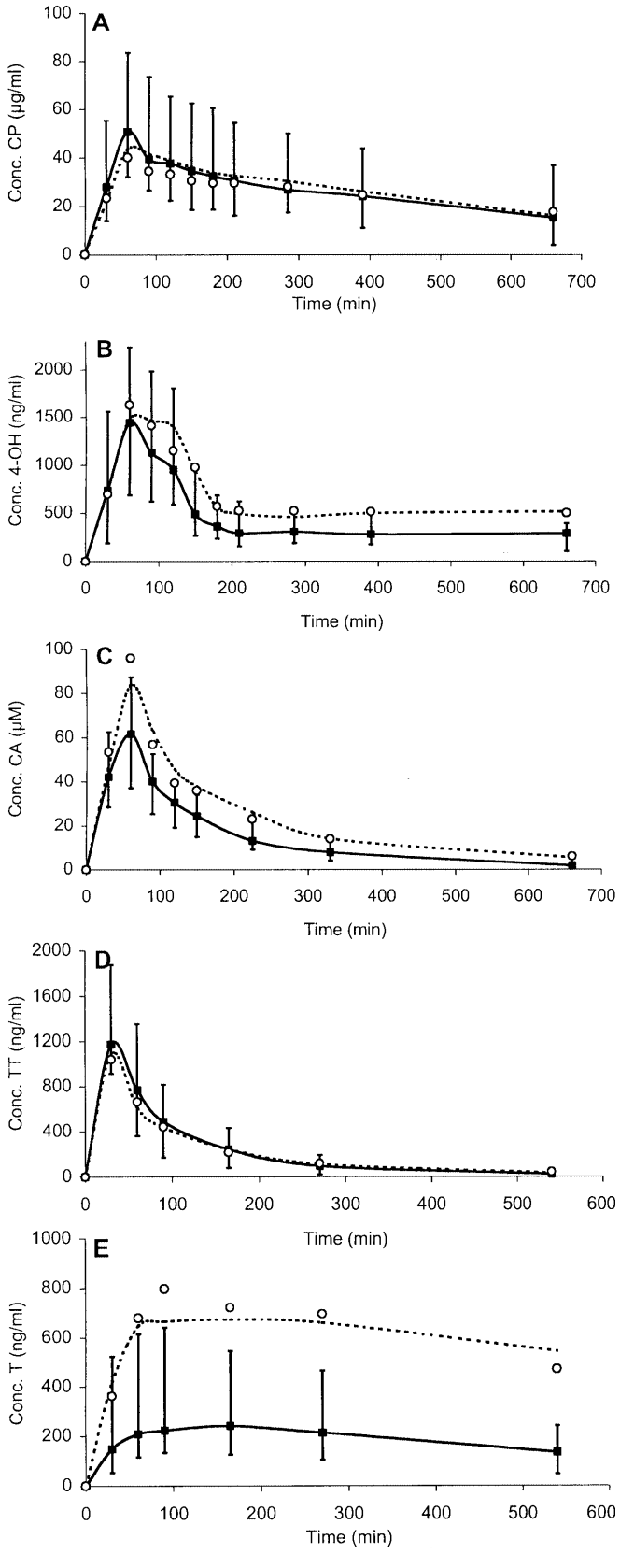

Fig. 1A–E. Concentration-time curves of cyclophosphamide (**A**), 4-hydroxycyclophosphamide (**B**), carboplatin (**C**), thiotepa (**D**) and tepa (**E**) for the obese patient (*circles*, the *dotted line* represents the individual Bayesian prediction) and the population (*squares*) (median and 2.5–97.5% percentiles)

patients with extreme obesity [23]. Similar results were found by Spinler et al. [22]. They concluded that Ccr estimates based on the Cockcroft-Gault formula in the obese are inaccurate using TBW (overprediction) or IBW (underprediction), but may be more accurate using ABW.

Other methods for estimating the Ccr, based on creatinine and other patient characteristics, were tested by Spinler et al. [22]. Almost all methods proved to be biased and imprecise in obese patients [21, 22]. Only the Salazar-Corcoran equation [19], developed for estimating Ccr in obese patients, using a corrected serum creatinine concentration, appeared to be unbiased and precise [19, 21, 22]. Conventional 24-h urine collection is used as the "gold standard" for the estimation of Ccr. However, this method is too time-consuming for use in daily practice, and questionable because it relies heavily on accurate measurement of urine volume per unit time. Chatelut et al. [5] developed a method for calculating the carboplatin clearance directly from creatinine and other patient characteristics. This method appears also to be able accurately to predict carboplatin clearance in obese patients if the Bénézet correction, using the mean value between IBW and actual body weight instead of TBW, is applied [3].

At present, there is no information available regarding the influence of obesity on the pharmacokinetics of cyclophosphamide, thiotepa and carboplatin. The question remains as to how initial doses of these compounds in obese patients should be calculated. General guidelines indicate that dosing of drugs with distribution restricted to lean tissues should be based on the IBW of patients. For drugs markedly distributed into fat tissue, the initial dose should be based on TBW [6].

For cyclophosphamide and thiotepa, it appears to be better to dose obese patients on the basis of IBW or ABW instead of TBW. In the described patient, dosing based on IBW (resulting in an adjusted BSA of 1.66 m^2 and respective cyclophosphamide and thiotepa doses of 1660 mg/day and 132 mg/day) would probably have resulted in exposures closest to those in the reference population. However, Przepiorka et al. recommend calculating the initial thiotepa dose in obese patients using ABW [14]. We therefore suggest basing both the initial cyclophosphamide and thiotepa doses in extremely obese patients on BSA calculated using ABW. In our case, the corrected BSA would have been 1.96 m^2, resulting in doses of 1960 mg/day and 156 mg/day, respectively. For carboplatin dosing, we recommend using the Cockcroft-Gault equation to estimate GFR, applying ABW in the calculation (also in view of the wide application of this formula in clinical practice). In this case, the Ccr would have been estimated as 123 ml/min, resulting in a carboplatin dose of 482 mg/day.

Because of the lack of a reliable method for chemotherapy dosing in obese patients, the use of TDM in this

patient group is of particular importance. Individual dosing may avoid excessively high exposures and may prevent severe toxicity. TDM in this patient, based on Bayesian estimates, resulted in downward dose adjustments of cyclophosphamide, thiotepa and carboplatin (44%, 50% and 42%, respectively) from the 3rd day of the course onwards, giving exposures comparable to those in the reference population and consequently reducing the treatment risk. Fortunately, the patient presented here did not develop any acute toxicity, nor, as far as can be judged, any long-term toxicities. This may be attributed to the intervention during the course.

In conclusion, this case suggests that the dose of cyclophosphamide, thiotepa and carboplatin in obese patients should be calculated using ABW instead of TBW to obtain exposures similar to this in patients with normal weight. Moreover, it seems clear that monitoring of plasma drug concentrations can be a useful tool for optimizing chemotherapy in obese patients.

Acknowledgements This work was supported by a grant from the Dutch Cancer Society (project NKI 2001-2420).

References

1. Ayash LJ, Wright JE, Tretyakov O, Gonin R, Elias A, Wheeler C, Eder JP, Rosowsky A, Antman K, Frei E III (1992) Cyclophosphamide pharmacokinetics: correlation with cardiac toxicity and tumor response. J Clin Oncol 10:995
2. Beal SL, Sheiner LB (1998) User's guides, NONMEM Project Group. University of California at San Francisco, San Francisco
3. Bénézet S, Guimbaud R, Chatelut E, Chevreau C, Bugat R, Canal P (1997) How to predict carboplatin clearance from standard morphological and biological characteristics in obese patients. Ann Oncol 8:607
4. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748
5. Chatelut E, Canal P, Brunner V, Chevreau C, Pujol A, Boneu A, Roché H, Houin G, Bugat R (1995) Prediction of carboplatin clearance from standard morphological and biological patient characteristics. J Natl Cancer Inst 87:573
6. Cheymol G (1993) Clinical pharmacokinetics of drugs in obesity. An update. Clin Pharmacokinet 25:103
7. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31
8. DuBois D, DuBois E (1916) A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17:863
9. Huitema AD, Spaander M, Mathôt RA, Tibben MM, Holtkamp MJ, Beijnen JH, Rodenhuis S (2002) Relationship between exposure and toxicity in high-dose chemotherapy with cyclophosphamide, thioTEPA and carboplatin. Ann Oncol 13:374
10. Hussein AM, Petros WP, Ross M, Vredenburgh JJ, Affronti ML, Jones RB, Shpall EJ, Rubin P, Elkordy M, Gilbert C, Gupton C, Egorin MJ, Soper J, Berchuck A, Clarke-Pearson D, Berry DA, Peters WP (1996) A phase I/II study of high-dose cyclophosphamide, cisplatin, and thiotepa followed by autologous bone marrow and granulocyte colony-stimulating factor-primed peripheral-blood progenitor cells in patients with advanced malignancies. Cancer Chemother Pharmacol 37:561
11. Moore MJ (1991) Clinical pharmacokinetics of cyclophosphamide. Clin Pharmacokinet 20:194
12. Petros WP, Broadwater G, Berry D, Jones RB, Vredenburgh JJ, Gilbert CJ, Colvin OM, Peters WP (1997) Correlation of high-dose cyclophosphamide, cisplatin, and carmustine pharmacokinetics to response and toxicity in patients with primary breast cancer (abstract). Proc ASCO 16:216a
13. Powis G, Reece P, Ahmann DL, Ingle JN (1987) Effect of body weight on the pharmacokinetics of cyclophosphamide in breast cancer patients. Cancer Chemother Pharmacol 20:219
14. Przepiorka D, Madden T, Ippoliti C, Estrov Z, Dimopoulos M (1995) Dosing of thiotepa for myeloablative therapy. Cancer Chemother Pharmacol 37:155
15. Rodenhuis S, Baars JW, Schornagel JH, Vlasveld LT, Mandjes I, Pinedo HM, Richel DJ (1992) Feasibility and toxicity study of a high-dose chemotherapy regimen for autotransplantation incorporating carboplatin, cyclophosphamide and thiotepa. Ann Oncol 3:855
16. Rodenhuis S, Westermann A, Holtkamp MJ, Nooijen WJ, Baars JW, Van der Wall E, Slaper-Cortenbach CM, Schornagel JH (1996) Feasibility of multiple courses of high-dose cyclophosphamide, thiotepa, and carboplatin for breast cancer or germ cell cancer. J Clin Oncol 14:1473
17. Rodenhuis S, Richel DJ, van der Wall E, Schornagel JH, Baars JW, Koning CCE, Peterse JL, Borger JH, Nooijen WJ, Bakx R, Dalesio O, Rutgers E (1998) Randomised trial of high-dose chemotherapy and haemopoietic progenitor-cell support in operable breast cancer with extensive axillary lymph-node involvement. Lancet 352:515
18. Rodenhuis S, De Wit R, De Mulder PHM, Keizer HJ, Sleijfer DT, Lalisang RI, Bakker PJM, Mandjes I, Kooi M, De Vries EGE (1999) A multi-center prospective phase II study of high-dose chemotherapy in germ-cell cancer patients relapsing from complete remission. Ann Oncol 10:1467
19. Salazar DE, Corcoran GB (1998) Predicting creatinine clearance and renal drug clearance in obese patients from estimated fat-free body mass. Am J Med 84:1053
20. Sawyer M, Ratain MJ (2001) Body surface area as a determinant of pharmacokinetics and drug dosing. Invest New Drugs 19:171
21. Snider RD, Kruse JA, Bander JJ, Dunn GH (1995) Accuracy of estimated creatinine clearance in obese patients with stable renal function in the intensive care unit. Pharmacotherapy 15:747
22. Spinler SA, Nawarskas JJ, Boyce EG, Connors JE, Charland SL, Goldfarb S (1998) Predictive performance of ten equations for estimating creatinine clearance in cardiac patients. Ann Pharmacother 32:1275
23. Van de Ree MA, Christiaan G, Huisman MV, Van der Vijver JCM, Meinders AE (2001) Monitoring renal function in obese patients with type 2 diabetes mellitus in daily practice. Diabetes Nutr Metab 14:66
24. Van Maanen MJ, Smeets CJM, Beijnen JH (2000) Chemistry, pharmacology and pharmacokinetics of N,N′,N″-triethylenethiophosphoramide (thiotepa). Cancer Treat Rev 26:257
25. Van Warmerdam LJC, Rodenhuis S, van der Wall E, Maes MA, Beijnen JH (1996) Pharmacokinetics and pharmacodynamics of carboplatin administered in a high-dose combination regimen with thiotepa, cyclophosphamide and peripheral stem cell support. Br J Cancer 73:979