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SHORT COMMUNICATION

Altered cyclophosphamide and thiotepa pharmacokinetics in a patient with moderate renal insufficiency

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Abstract
Purpose We report a patient with renal insufficiency (creatinine clearance, CL_{cr} = 38 mL/min) who received high-dose chemotherapy with cyclophosphamide (1,500 mg/m^2 day^{-1}), thiotepa (120 mg/m^2 day^{-1}) and carboplatin (AUC = 5 mg min/mL day^{-1}) for four consecutive days.
Methods Blood samples were collected on day 1 and 3 and plasma levels of cyclophosphamide, its active metabolite 4-hydroxycyclophosphamide, thiotepa, its main metabolite tepa and carboplatin were determined.
Results Pharmacokinetic analyses indicated that the elimination of cyclophosphamide, thiotepa, carboplatin, but especially tepa was strongly reduced in this patient, resulting in increased exposures to these compounds of 67, 43, 30 and 157%, respectively, compared to a reference population (n = 24) receiving similar doses. Exposure to 4-hydroxycyclophosphamide increased 11%.
Conclusion These results suggest that it may not be necessary to alter the dose of cyclophosphamide in patients with moderate renal impairment. However, because high exposures to thiotepa and tepa have been correlated with increased toxicity, caution should be applied when administering thiotepa to patients with renal insufficiency.

Keywords Renal insufficiency · Cyclophosphamide · Thiotepa · Pharmacokinetics

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Introduction

Cyclophosphamide and thiotepa are alkylating agents that belong to the most frequently used cytotoxic agents in high-dose chemotherapy regimens. A regimen that is commonly used in the Netherlands is the CTC regimen, which consists of cyclophosphamide (6,000 mg/m^2), thiotepa (480 mg/m^2) and carboplatin (1,600 mg/m^2) divided over 4 days administered in short infusions [1].

When using chemotherapeutic agents at the limit of non-haematological toxicity, there is a substantial risk of adverse outcome. 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. Various relations between exposure and toxicity or even efficacy have been identified [2].

Cyclophosphamide is a prodrug that needs to be activated by cytochrome P450 to 4-hydroxycyclophosphamide, which is the main route of metabolism. Both the metabolites and 12–30% of unchanged parent compound are eliminated in the urine [3]. Thiotepa is rapidly metabolised by cytochrome P450 to tepa, its main and active metabolite. Thiotepa and tepa have similar alkylating properties. Less than 2% of the administered dose of thiotepa is eliminated unchanged in the urine. Renal elimination of tepa accounts for approximately 11% of the administered dose [4, 5]. Carboplatin is a platinum compound, with renal elimination

accounting for almost all drug elimination. In patients with normal renal function, between 60 and 70% of an administered dose is excreted in the urine within the first 24 h of administration [6].

Renal insufficiency is a factor that may complicate drug dosing. When renal function is compromised, drug and metabolites eliminated through the kidneys will retain in the body and may accumulate to toxic levels with repeated dosing. Scarce information is available about the pharmacokinetics of (high dose) cyclophosphamide and thiotepa in patients with renal insufficiency. Earlier studies have described the pharmacokinetics of cyclophosphamide in adults with renal dysfunction receiving either standard dose [7–11] or myeloablative doses of cyclophosphamide [12, 13]. However, data are controversial. Minimal effects of renal dysfunction upon cyclophosphamide AUC have been reported [8, 11, 12], while others have shown an elevated AUC in those with impaired renal function [9, 10, 13]. A report in an anephric child indicated that off haemodialysis clearance of cyclophosphamide was similar to cyclophosphamide clearance in children with normal renal function [14]. Studies reporting the impact of renal dysfunction upon the metabolites of cyclophosphamide show that plasma alkylating activity was increased in patients with renal failure [7, 10, 11].

It has been shown that carboplatin clearance is decreased in patients with decreased renal function, resulting in increased toxicity [15]. Dose adjustment of carboplatin is required in these patients. The Calvert formula is widely used for carboplatin dosing based on the glomerular filtration rate [16].

In this report we describe the pharmacokinetics of cyclophosphamide, its active metabolite 4-hydroxycyclophosphamide, thiotepa, its active metabolite tepa and carboplatin in a patient with renal insufficiency.

Patients and methods

Case

A 40-year-old male patient was diagnosed with Ewing sarcoma. As part of his treatment he received one course of high-dose chemotherapy with autologous peripheral blood progenitor cell transplantation, consisting of cyclophosphamide (1,500 mg/m^2 day^{-1}) as 1-h infusion, immediately followed by carboplatin [dose calculated based on modified Calvert formula: AUC (mg min/mL) = Dose (mg)/(CL_{cr} (mL/min) + 25) with 5 mg min/mL as daily target AUC] as 1-h infusion and thiotepa (120 mg/m^2 day^{-1}) divided over two 30-min infusions 12 h apart, for four consecutive days. Full details of the CTC regimen have been published previously [17].

The patient had normal cardiac, hepatic, haematopoietic and pulmonary function. Renal function was, however, impaired (calculated creatinine clearance 38 mL/min, using the Cockcroft–Gault equation [18]).

Pharmacokinetic analysis

For pharmacokinetic analyses, blood samples were collected from a double lumen intravenous catheter inserted in a subclavian vein. Samples were collected on day 1 and 3 prior to the start of the infusions, at 30 min after the start of cyclophosphamide infusion ($t = 30$) and $t = 60$ (end of cyclophosphamide infusion), 90, 120 (end of carboplatin infusion), 150 (end of thiotepa infusion), 180, 210, 285, 390 and 660 min. Samples were processed as described previously [19–21]. Analytical methods used for the determination of plasma concentrations of cyclophosphamide, 4-hydroxycyclophosphamide, thiotepa, tepa and carboplatin have been reported previously [19–21].

Population pharmacokinetic models of carboplatin, cyclophosphamide (and its metabolite 4-hydroxycyclophosphamide) and thiotepa (and its metabolite tepa) were used for calculating the pharmacokinetic parameters of all compounds using Bayesian analysis [2, 22]. The pharmacokinetic parameters of the different compounds in this patient were compared with the respective median values in a reference population of patients ($n = 24$) who also received CTC and were dosed (except for carboplatin, reference population received 400 mg/m^2 day^{-1}) and sampled as described above. Complete pharmacokinetic profiles of the reference population were available of day 1 and day 3 or 4. Exposure was defined as the cumulative exposure of the 4-day course extrapolated to infinity. The protocol was approved by the Committee on the Medical Ethics of the Netherlands Cancer Institute and written informed consent was obtained from the patient.

Results

Administration of cyclophosphamide, thiotepa and carboplatin in this patient led to increased exposures to all compounds. Table 1 shows the median cumulative exposures following one course in both the population and the patient, the latter based on the pharmacokinetics obtained on the first day of the 4-day course. Figure 1 shows the plasma concentration–time data of the patient versus the typical plasma concentration–time curve of the reference population [2, 22].

Comparing pharmacokinetic parameters of cyclophosphamide, thiotepa and carboplatin in this patient with those in the reference population, it appeared that the renal clearance of cyclophosphamide and thiotepa decreased

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

Compound	AUC units	AUC patient	Median AUC reference population	2.5–97.5% range	Deviation (%)
Cyclophosphamide	uM h	11,467	6,871	4,355–10,664	67
4-Hydroxycyclophosphamide	uM h	157	142	105–186	11
Thiotepa	uM h	185	129	81–201	43
Tepa	uM h	648	252	108–427	157
Thiotepa and tepa	uM h	833	384	222–584	117
Carboplatin	mg min/mL	26	20[a]		30

[a] Target AUC value, reference population received carboplatin dose of 400 mg/m^2 day^{-1}

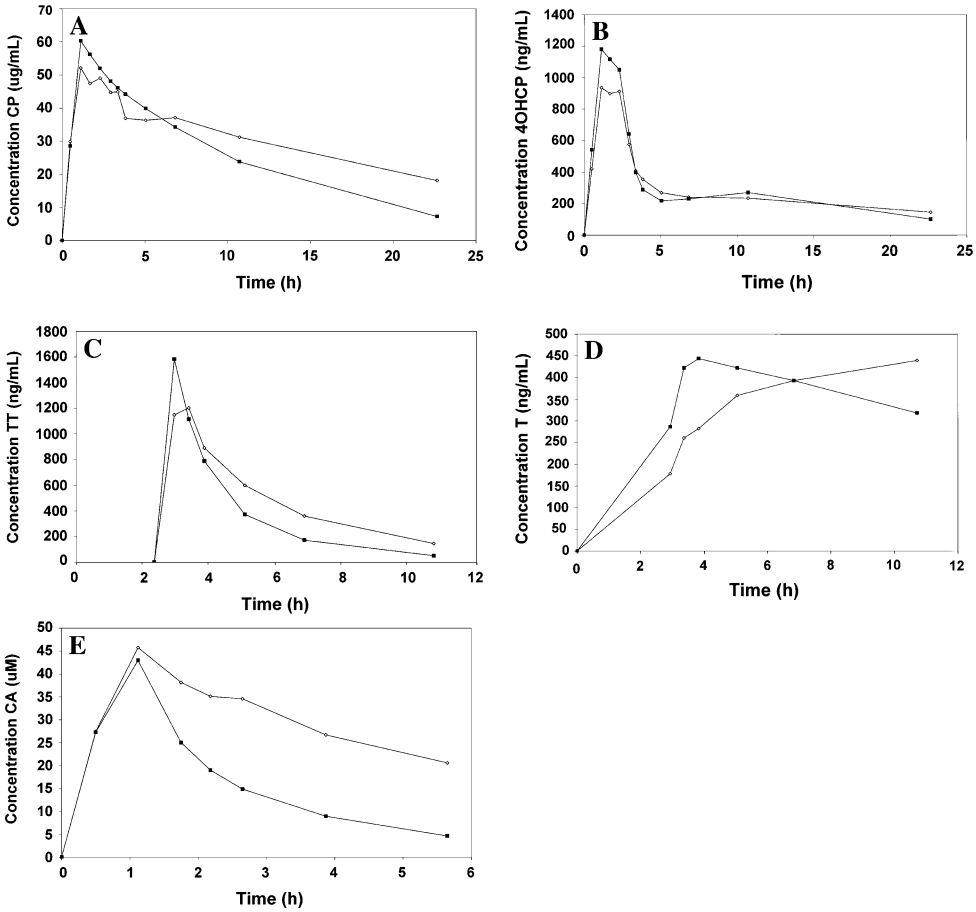

Fig. 1 Concentration–time curves of **a** cyclophosphamide (CP), **b** 4-hydroxycyclophosphamide (4OHCP), **c** thiotepa (TT), **d** tepa (T) and **e** carboplatin (CA) with *triangle* representing the patient and *filled square* the typical plasma concentration–time curve of the reference population

in the patient compared to the reference population with 28 and 36%, respectively (2.1 vs. 2.9 L/h and 15.9 vs. 24.9 L/h). This resulted in an increased exposure to cyclophosphamide and thiotepa of 67 and 43%, respectively. Exposure to 4-hydroxycyclophosphamide was only moderately increased, due to a minor decrease in elimination of 4-hydroxycyclophosphamide (7%) and a minor increase in metabolic fraction (11%), compared to the reference population. Exposure to tepa, however, increased dramatically (157%), mainly due to a decreased elimination rate constant of tepa (0.23 h^{-1} in the patient vs. 0.47 h^{-1} in the reference population). Although carboplatin was dosed based on creatinine clearance the exposure was still 30% above the target value (26 vs. 20 mg min/mL).

Based on the pharmacokinetic analyses of day 1 of the course, the doses of cyclophosphamide, thiotepa and carboplatin were reduced on days 3 and 4 to reach a predefined target exposure (the median exposure in a reference population receiving similar doses) [23]. The cyclophosphamide dose was reduced from 2,955 to 2,550 mg/day, the thiotepa dose from 236 to 162 mg/day and the carboplatin dose from 315 to 275 mg/day. This resulted in an exposure closer to

the target exposure. Combined exposure to thiotepa and tepa, however, was still 75% above the target. Renal function remained the same during the 4 days of chemotherapy.

The patient experienced grade 3 mucositis and diarrhoea. Furthermore, grade 2 aspartate aminotransferase (ASAT) and bilirubin toxicity was observed. In the reference population three patients experienced grade 3 mucositis (12.5%), no patients had grade 3 diarrhoea, six patients experienced grade 2 ASAT toxicity (25%) and one patient had grade 2 bilirubin toxicity (4.2%). On day 43 post-transplantation the patient died due to acute respiratory distress syndrome.

Discussion

Renal insufficiency alters the pharmacokinetics of drugs. If drugs or their active metabolites are excreted by the kidneys they can accumulate in patients with renal insufficiency. In the patient reported here, increased exposures to cyclophosphamide, 4-hydroxycyclophosphamide, thiotepa, tepa and carboplatin were observed.

The patient described here experienced excessive exposure to tepa. Renal elimination of thiotepa accounts for only a small part of its elimination, for tepa, apparently, renal elimination is an important route. Toxicities associated with thiotepa treatment are mainly mucositis and central nervous system toxicity. The most frequently affected organs being the liver and gastrointestinal tract, resulting in nausea, vomiting and diarrhoea [4]. Moreover, a relation between ASAT toxicity and thiotepa AUC has been demonstrated [2]. Indeed, this patient experienced severe mucositis and diarrhoea and grade 2 ASAT toxicity, probably due to excessive exposure to thiotepa and tepa.

Clearance of cyclophosphamide was reduced, which resulted in an increase in cyclophosphamide exposure. Since cyclophosphamide itself is not active, increases in exposure to the active metabolites are more important for the interpretation of the clinical relevance of this effect. The exposure to 4-hydroxycylophosphamide was only moderately increased, indicating no need to adjust the dose of cyclophosphamide in patients with moderate renal insufficiency. Our data are in agreement with the data of Juma et al. [10] who reported a lower clearance (−17%) and an increase in half-life (+24%) of cyclophosphamide in five patients with moderate to severe renal insufficiency (creatinine clearances 18–51 mL/min) compared to eight matched controls with normal renal function. Similar results were reported by Haubitz et al. [9] who found a lower clearance (−28%) of cyclophosphamide in patients with creatinine clearances of 25–50 mL/min, which resulted in an increase in systemic drug exposure of 38%. Mouridsen et al. [11] showed that the biotransformation rate is unaffected in patients with renal impairment. Bramwell et al. [8] could not demonstrate a correlation between renal function and clearance of cyclophosphamide or its alkylating metabolites due to the large inter-individual variability in cyclophosphamide break-down seen in that study. Further data regarding the impact of renal dysfunction upon the metabolites of cyclophosphamide are scarce. One study showed that total alkylating activity as measured by the nitrobenzylpyridine (NBP) reaction was significantly increased in renal failure [10]. However, this NBP reaction is highly non-specific and variable [24]. Therefore, no firm conclusions could be attributed to this result. A report about cyclophosphamide disposition in an anephric child showed that the exposure to 4-hydroxycylophosphamide off haemodialysis was in the same range as our results [14]. Clinically relevant changes in cyclophosphamide pharmacology due to alterations in renal function have not been demonstrated.

For carboplatin it is known that renal insufficiency causes increased exposure to carboplatin. Therefore, a priori dose adjustments of carboplatin are performed. Although this patient had an adjusted dose of carboplatin based on his creatinine clearance, exposure to carboplatin was still 30% above the target exposure. Substitution of the glomerular filtration rate in the Calvert formula by an estimate of creatinine clearance calculated using the Cockcroft–Gault equation led to an overestimation of the carboplatin clearance in this patient. Froissart et al. [25] showed that the use of the Cockcroft–Gault equation can lead to overestimation of the glomerular filtration rate in patients with GFR <60 mL/min.

In conclusion, this case report demonstrates the pharmacokinetic disposition of cyclophosphamide, 4-hydroxycyclophosphamide, thiotepa, tepa and carboplatin in a patient with reduced renal function. Renal insufficiency in this patient resulted in a high exposure to thiotepa and especially tepa and is, therefore, of potential clinical importance. Additional pharmacokinetic and pharmacodynamic data are warranted in future studies to provide more accurate dosage recommendations for thiotepa in these patients.

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