Population pharmacokinetics of topotecan: intraindividual variability in total drug

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Abstract The inter- and intraindividual variabilities in topotecan clearance (CL) were explored using a population pharmacokinetic approach. Total (lactone + hydroxy acid) topotecan plasma concentrations were obtained in 31 women with metastatic epithelial ovarian cancer treated by the 30-min intravenous infusion on 5 subsequent days. The data corresponding to three occasions (days 1 and 5 of cycle 1, and day 1 of cycle 2), were analyzed using the nonlinear mixed effect model program. A large interindividual variability was observed, with CL varying from 9.1 to 42.5 l per hour (mean 21.0). Topotecan CL was related to serum creatinine level, and age. A close relationship was also observed between topotecan CL and creatinine clearance. Intraindividual variability both within cycle 1 and between the two first cycles was limited, with a mean variation of $-2 \pm 17\%$, and $+5 \pm 20\%$, respectively. A limited sampling strategy using Bayesian estimation based on two samples (5 min before the end of the 30-min infusion, and 4 h after the end of infusion) was developed. The results of this study combine relationships between topotecan pharmacokinetic parameters and patient covariates that may be useful for a priori dose adjustment, and convenient sampling procedure that can be used for further studies and drug monitoring.

Key words Topotecan · Nonlinear mixed effect model · Population pharmacokinetics · Therapeutic drug monitoring

Abbreviations AUC Area under the curve · CL Topotecan clearance · CrCl Creatinine clearance · EO1 End of the infusion · HPLC High-performance liquid chromatographic · NONMEM Nonlinear mixed effect model · Scr Serum creatinine

Introduction

Topotecan (9-dimethylaminomethyl-10-hydroxycamptothecin) is a water-soluble semisynthetic analogue of camptothecin that binds to the topoisomerase I–DNA complex, leading to single-stranded, protein-associated DNA breakage and cellular cytotoxicity. Topotecan (Hycamtin) was approved in 1996 for the treatment of ovarian cancer patients following failure of first-line therapy. The dose-limiting toxicity of topotecan is myelosuppression, predominantly neutropenia [18]. The drug is poorly bound to plasma proteins, but is present under open hydroxy acid and closed lactone forms within the plasma according to a relatively constant ratio determined primarily by pH [11]. Several studies have shown pharmacokinetic-pharmacodynamic relationships for topotecan [9]. For the most used schedule (i.e., 30-min intravenous infusion on 5 subsequent days every 3 weeks), a correlation has been shown between the total (i.e., lactone plus hydroxy acid forms) plasma area under the curve (AUC) observed on day 1 and the percentage decrease in white blood cells [8, 15, 16, 20]. In keeping with these previous reports, we performed a clinical trial with dose individualization of topotecan based on a pharmacokinetic exploration during cycle 1 (days 1 and 5) and cycle 2 (day 1). The methodology of
the study consisted of individual analysis of the topotecan plasma concentrations versus time. The conventional pharmacokinetic parameters (i.e., obtained by individual analysis) and toxicity results will be presented elsewhere. After completion of this trial, we analyzed the data according to a population approach using the nonlinear mixed effect model (NONMEM) program [1] to describe more accurately the inter- and intridual pharmacokinetic variabilities, to examine the correlation between pharmacokinetic parameters and patient covariates, and to develop a limited sampling strategy for determining topotecan clearance (CL).

Materials and methods

Patients and treatment

Pharmacokinetic evaluation was performed in 31 women with metastatic epithelial ovarian cancer previously treated with at least one platinum-containing chemotherapy regimen; of these, 26 had been pretreated by cisplatin. Patient characteristics are presented in Table 1. Topotecan (Hycamtin, SmithKline Beecham Laboratories, USA) provided as the hydrochloride salt. This was dissolved in 100 ml 5% dextrose solution and administered intravenously by an automatic infusion pump over 30 min, repeated for 5 consecutive days every 3 weeks. In cycle 1 the daily dose for the 3 first days corresponded to the standard recommendation: 1.5 or 0.75 mg/m² per day if the patient creatinine clearance (CrCl calculated according to Cockcroft-Gault equation [5]) was greater than 40 or between 20 and 40 ml/min, respectively. The daily dose for the last 2 days of cycle 1 depended the observed topotecan AUC on day 1; the general objective was to constrain the overall AUC (i.e., from day 1 to day 5) within 37,500–75,000 nM/min (263–527 μg/l per hour). In patients with AUC on day 1 greater than 15,000 nM/min the daily dose for the last 2 days was decreased to achieve an overall AUC of 75,000 nM/min. In patients with AUC on day 1 lower than 7500 nM/min the daily dose for the last 2 days was increased to achieve an overall AUC of 37,500 nM/min. In patients with CrCl on day 1 between 7500 and 15,000 nM/min no dose modification was performed during cycle 1. In cycle 2 the daily dose was 75%, 100%, or 125% of the mean daily dose of cycle 1 in patients with dose-limiting toxicity, with minor toxicity, or without toxicity, respectively, during the intercycle period.

Blood sampling and topotecan analysis

A pharmacokinetic exploration was performed on days 1 and 5 (except for three patients for whom the treatment was stopped after 3 days because of high topotecan AUC on day 1) of cycle 1, and day 1 of cycle 2 (except for six patients not treated because of toxicity or deterioration of their performance status due to the disease progression). Blood samples were taken immediately before, 5 min before the end of the 30-min infusion, and 0.5, 1, 2, 4, 8 h after the end of infusion. Blood samples (3 ml in heparinized tubes) were collected using an indwelling intravenous cannula placed in the opposite arm. After immediate centrifugation at 1500 g for 10 min, at 4 °C, the plasma was separated and stored (−20 °C) until analysis. The total (i.e., lactone plus hydroxy acid forms) topotecan levels were determined using high-performance liquid chromatographic (HPLC) method previously described [17]. The limit of quantification was 0.5 μg/l plasma. A cross-validation was performed within the four sites of HPLC analysis (Toulouse, Montpellier, St-Herblain, and St-Cloud) using four seeded plasma control samples with nominal values from 1.15 to 65.5 μg/l; the intercenter coefficients of variation for precision ranged between 6% and 15%. These seeded were used as quality control to validate each HPLC assay; the obtained concentrations should be within ±10% of the nominal values (±15% for the lowest quality control).

Pharmacokinetic analysis

Total topotecan plasma levels were analyzed according to a two-compartment model with linear elimination from the central compartment using NONMEM [3] (version V, level 1.1) with the first-order conditional estimation method and the PREDPP package [2] running on a personal computer. A proportional error model was used for the interpatient variabilities. A combination model (i.e., additive plus proportional) was used for residual variability.

Intridual variabilities

The intridual variabilities in CL between days 5 and 1 of cycle 1, and between day 1 of cycle 2 and day 1 of cycle 1 were both evaluated by using the interoccasion variability as described by Karlsson and Sheiner [12]. This model takes account of random variability in subject’s parameters between study occasions and allows one to obtain a specific value of CL for each occasion. The intrapatient variability in clearance within cycle 1 (data available in 28 patients) was expressed as the percentage variation between day 5 and day 1: (CL_{day 5} – CL_{day 1}) × 100/CL_{day 1}. The percentage variation between the CL on day 1 of cycle 2 (data available in 25 patients) and that on day 1 of cycle 1 was also evaluated to evaluate the pharmacokinetic variability between cycles.

Relationships between covariates and pharmacokinetic parameters

Six patient covariates were tested using the data from all patients (n = 31) on day 1 of cycle 1: weight, body surface area calculated according to the Dubois formula [6], age, WHO performance status score, serum creatinine (Scr), and CrCl calculated according to the Cockcroft-Gault equation [5]. In fitting the data, NONMEM computed the value of a statistical function and the minimial value of the objective function, which is equal to minus twice the log likelihood. For testing of the covariates the different models were compared using the approximation to the χ² distribution of the objective function value of the reduced model (e.g., model without covariate) minus that of the full model (e.g., model with covariate); the number of degrees of freedom was equal to the difference in the number of parameters between two nested models. For example, a difference in the objective function larger than 3.8 (associated with a P < 0.05 and 1 degree of freedom) was required to consider the model without covariate more appropriate than the model with the covariate.

Development of a limited sampling strategy to estimate topotecan clearance

The patients were randomized into two groups: 16 in the reference group and 15 in the test group. Bayesian estimation was performed using the NONMEM program to determine the CL of test group patients from a limited number of samples. The data base consisted of the data of the reference group patients. Regarding the previous report showing a close relationship between CL and CrCl [16], for all patients (i.e., both reference and test groups) Cockcroft-Gault

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age (year)</td>
<td>61</td>
<td>47–76</td>
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<tr>
<td>Body surface area (m²)</td>
<td>1.62</td>
<td>1.36–1.86</td>
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<tr>
<td>Weight (kg)</td>
<td>61</td>
<td>46–85</td>
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<tr>
<td>Serum creatinine (μmol/l)</td>
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<td>45–140</td>
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<td>Creatinine clearance (ml/min)</td>
<td>64</td>
<td>35–126</td>
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<tr>
<td>Bilirubin (μmol/l)</td>
<td>9</td>
<td>2–22</td>
</tr>
</tbody>
</table>

a Calculated according to the Dubois formula [6]
b Calculated according to the Cockcroft-Gault equation [5].