Individual Adaptive Dosing of Topotecan in Ovarian Cancer

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ABSTRACT

Purpose: To take into account relationships between topotecan area under the plasma concentration (AUC) versus time curve and percentage decrease of neutrophil count previously shown when topotecan is administered on a 5-day, daily schedule. A multicentric clinical trial with individualized dosing of topotecan was performed in patients with platinum-refractory ovarian cancer. The primary goal of this study was to evaluate the toxicity of topotecan when the interindividual variability in plasma drug exposure is decreased.

Experimental Design: A total of 39 patients were evaluable. In cycle 1, the daily dose for the last 2 days was dependent on the observed topotecan AUC at day 1; the general objective was to constrain the overall AUC (i.e., from day 1 to day 5) within 37,500–75,000 nMmin. A pharmacokinetic study was also performed on day 5 of cycle 1 and day 1 of cycle 2 to evaluate the intrapatient pharmacokinetic variability both within cycle 1 and between cycles.

Results: The dose of topotecan was decreased for 20 patients and increased for only 1 patient within cycle 1. The total administered dose was correlated to the creatinine clearance. The dose adjustments allowed control of the topotecan exposure: mean (±SD) observed AUC of 70,697 (±12,364) nMmin. Fourteen cases of dose-limiting toxicity were observed, mainly in patients who previously received two different regimens of chemotherapy without a washout period before topotecan treatment. An overall response rate of 21% was observed in the 33 evaluable patients.

Conclusion: Dose adjustments are required not only in patients with creatinine clearance below 40 ml/min, but also in those with values between 40 and 60 ml/min (recommended starting dose is 1.2 mg/m²). By performing drug monitoring and taking into consideration the past treatment of each patient, better dose individualization can be obtained.

INTRODUCTION

Topotecan, 9-dimethylaminomethyl-10-hydroxycamptothecine, is a water-soluble semisynthetic analogue of camptothecin that binds to topoisomerase I-DNA complexes, leading to single-stranded, protein-associated DNA breakage and cellular cytotoxicity. Topotecan (Hycamint) was approved in 1996 for the treatment of ovarian cancer patients after first-line therapy failure. The drug is poorly bound to plasma protein but is present under open hydroxy-acid and closed lactone forms within the plasma according to a relatively constant ratio determined primarily by pH (1). Approximately 50% of topotecan are excreted unchanged in the urine (2). Some metabolites, such as N-desmethyl topotecan, are formed by hepatic oxidative metabolism (3). The topotecan CL presents a large interindividual variability (ranging from 65 to 587 ml/min/m²) with a coefficient of variation of 38% (4, 5). Alteration of elimination was observed in patients with impaired renal function (6, 7), whereas mean plasma CL did not differ significantly between patients with or without liver injury (8). The DLT of topotecan is myelosuppression, predominantly neutropenia. The maximum tolerated dose is dependent on the schedule of administration, as is expected for a cytotoxic drug with S phase specificity (9, 10). Once a particular schedule is considered, several studies have shown the correlation between the total (i.e., lactone plus hydroxy-acid forms) topotecan plasma AUC and the percentage decrease in WBCs (11). In the most frequently used schedule (i.e., 30-min i.v. infusion on 5 subsequent days every 3 weeks), total AUC (i.e., from day 1 to day 5) higher than 75,000 nMmin was associated with a high probability of major toxicity, whereas patients with total AUC lower than 37,500 nMmin presented a limited decrease in neutrophil count (5, 6, 8, 12). To take into account these previous observations, a multicentric clinical trial with individualized dosing of topotecan was performed in patients with platinum-refractory ovarian cancer. The primary goal of this study was to evaluate the toxicity of topotecan when the interindividual variability in plasma drug exposure is decreased.

PATIENTS AND METHODS

Patient Selection. Eligibility requirements for participation in this study included histological documentation of metastatic epithelial ovarian cancer in women who had been treated previously with at least one platinum-containing chemotherapy...
regimen. Eligible patients were required to have the following laboratory values: granulocyte count $\geq 1,500/\mu l$ and platelet count $\geq 100,000/\mu l$. A WHO performance status less than or equal to 2 was required. All patients gave written informed consent to participate in this protocol, as approved by the regional ethical committee.

**Treatment Plan.** Topotecan (Hyacint; GlaxoSmith-Kline, Philadelphia, PA), provided as the hydrochloride salt, was dissolved in 100 ml of 5% dextrose solution and administered i.v. by an automatic infusion pump over 30 min, repeated for 5 consecutive days every 3 weeks.

In cycle 1, the daily dose for the first 3 days was dependent on the patient creatinine clearance [CrCl, calculated according to the Cockcroft-Gault equation (13)], according to the guidelines defined by the manufacturer: 1.5 mg/m$^2$/day when CrCl was greater than 40 ml/min and 0.75 mg/m$^2$/day when CrCl was between 20 and 40 ml/min. The daily dose for the last 2 days of the cycle was dependent on 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$^{-1}$·h). For patients with an AUC at 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 by using the value of the topotecan CL on day 1. For patients with an AUC at day 1 less than 7,500 nM·min, the daily dose for the last 2 days was increased to achieve an overall AUC of 37,500 nM·min. For patients with an AUC at day 1 between 7,500 and 15,000 nM·min, no dose modification was performed during cycle 1.

In cycle 2, the daily dose for the first 3 days was adapted according to the total dose administered during the first cycle and the toxicity observed during cycle 1. When a DLT occurred (defined as neutrophils $< 500/mm^3$ during 7 or more days, or neutrophils $< 500/mm^3$ associated with fever or infection, or platelets $< 25,000/mm^3$), the daily dose was equal to a 25% decrease of the mean daily dose of cycle 1. In case of minor toxicity during cycle 1, the same mean daily dose as in cycle 1 was administered. In case of no toxicity (defined as WHO grade 0 for nonhematological toxicity, and grade 0–1 for hematological toxicity), the daily dose was equal to a 25% increase of the mean daily dose of cycle 1. For the last 2 days of cycle 2, the daily dose was modified only if the topotecan CL determined at day 1 of cycle 2 was significantly lower (i.e., $< 75\%$) than that of day 1 of cycle 1: a decreased dose was administered at days 4 and 5 to obtain a total dose for cycle 2 in proportion to the diminution of CL between cycles.

For the following cycles, the only criterion for the dose calculation was the tolerance during the inter-cycle period: 75% or 125% of the mean daily dose in the case of DLT or no toxic effect, respectively; the dose was not changed in other cases. Patients were treated if granulocyte count was $\geq 1,500/\mu l$ and platelet count was $\geq 100,000/\mu l$.

**Blood Sampling and Topotecan Analysis.** For each patient, a pharmacokinetic exploration was performed at day 1 and day 5 of cycle 1, and day 1 of cycle 2. Each day, blood samples were taken immediately before the 30-min infusion, as well as 5 min before, and 0.5, 1, 2, 4, and 8 h after the end of the infusion. Blood samples (4 ml in heparinized tubes) were collected using an indwelling i.v. cannula placed in the arm not receiving chemotherapy. After immediate centrifugation at 1500 $\times$ g for 10 min at 4°C, the plasma was separated and stored ($-20\°$C) until analysis. The topotecan levels were determined using HPLC as previously described (14). The limit of quantification was 0.5 µg/liter of plasma. A cross-validation was performed within the four centers of HPLC analysis (Toulouse, Montpellier, Nantes, and Saint-Cloud) using four seeded plasma control samples with nominal values from 1.15 to 65.5 µg/liter: the inter-center coefficients of variation for precision ranged between 6% and 15%. These seeded plasmas were used as quality control to validate each HPLC assay: the obtained concentrations should be within $\pm 10\%$ of the nominal values ($\pm 15\%$ for the lowest quality control).

**Pharmacokinetic Analysis.** The pharmacokinetic analysis of the topotecan plasma concentration versus time was fitted to a weighted ($1/y^2$) least-squares criterion by using the computer program Sifhar (Simed, Créteil, France). Pharmacokinetic parameters were computed from the modeled data: the AUC was calculated as the exact integral of the concentration-time curve from zero to infinity. For cycle 1, the total (i.e., from day 1 to day 5) observed AUC was calculated by dividing the total dose ($3 \times $Dose$_{day\,1}$ + $2 \times $Dose$_{day\,5}$) by the mean CL [($CL_{day\,1}$ + $CL_{day\,5}$) $\times$ 0.5].

**Follow-up Studies.** Complete blood counts were obtained on days 5, 8, 10, 15, and 17, as well as on every other day if the absolute neutrophil count was less than 1000/µl. Tumor measurements were performed after every two courses of treatment. Patients were allowed to continue therapy if they had not developed progressive disease (defined as the appearance of one nonhematological lesion or a 50% or greater increase in the products of the bidimensional diameters of any measurable lesion). For patients with more than two cycles, final evaluation of the antitumor activity was performed. A response was deemed partial if 50% or greater reduction was observed in the sum of the products of the bidimensional diameters of all measurable lesions when documented by two measurements separated by at least 6 weeks.

**RESULTS**

**Patients and Initial Dosing**

A total of 40 eligible patients were initially entered into the study, but one was excluded because blood samples could not be performed. The patient characteristics are given in Table 1. Six patients required an initial daily dose of 0.75 mg/m$^2$ because of
AUC of 37,500 nM in 39 patients. In one case, the dose was increased to reach an overall dose of 6.3 mg/m² (range: 3.1–9.4) at cycle 1 and cycle 2, respectively. Among the 12 patients with initial reduced dose due to impaired renal function, 2 patients required an additional dose reduction (Fig. 1). Among the 12 patients with CrCl ranging between 40 and 60 ml/min, 10 required a diminution of dose, whereas, among the 11 patients with values greater than 80 ml/min, only 2 did. Overall, the mean total dose administered was 6.3 mg/m² (range: 3.1–9.4) and 5.8 mg/m² (range: 2.7–8.9) at cycle 1 and cycle 2, respectively. Among the 33 who received a second cycle, 3 patients required a dose reduction during cycle 2 due to significant decrease of topotecan CL between cycles.

Toxicity

Cycle 1. DLT was observed in 14 of 39 patients, neutropenia in 12 cases, and/or thrombocytopenia in 5 cases; and one toxicity-related death was noted in a patient for whom the total dose had been decreased to 6.6 mg/m². Table 3 shows the mean topotecan AUC of patients classified according to two criteria: dose decrease and observed toxicity. The same percentage of DLT occurred with or without a dose decrease. However, a significant difference was observed when the AUC was compared in patients with or without toxicity (P = 0.048). Moreover, a detailed retrospective comparison between toxicity and patient characteristics showed that the occurrence of DLT appeared to be dependent on the number of regimens of chemotherapy administered after the last 6-month wash-out period (without chemotherapy) and before topotecan treatment: 2 of 15 patients who did not receive any chemotherapy within the 6 months preceding topotecan experienced DLT, as did 4 of 13 patients with one regimen, and 8 of 11 patients with two or more successive regimens (P < 0.05, χ² test).

Cycle 2 and Others. Thirty-three patients received more than one cycle. The median number of cycles was four (maximum, seven). Cycle 2 was delayed 1 and 2 weeks in 5 patients and 1 patient, respectively. DLT was observed in only three patients after cycle 2; consequently, the dose for the following cycle was again decreased. For the other patients, the doses of the following cycles (overall number, 84) were identical to those of cycle 2, and only two cycles were delayed due to toxicity.

Pharmacokinetics

Plasma concentrations of total topotecan were best described using a two-compartment model (98 cycles) or a one-compartment model (8 cycles). The mean topotecan CLs are summarized in Table 2. There was no significant difference (paired Student’s test) between topotecan CL at day 1 and day 5 of cycle 1 (P = 0.67), or between those at day 1 of cycle 1 and day 1 of cycle 2 (P = 0.26), indicating the absence of systematic change of CL with time. Topotecan CL was slightly but significantly correlated with creatinine clearance (Fig. 1). By comparison, topotecan CL was not correlated with body surface area (r² = 0.04, not significant). Fig. 2 shows that the observed total AUC at cycle 1 was very close to the total AUC predicted according to the CL at day 1.

Dose Modifications

Dose modification during cycle 1 affected 21 of 39 patients. In one case, the dose was increased to reach an overall AUC of 37.500 nM/min. In the other 20 patients, the dose was decreased: for 3 patients, the treatment was stopped after day 3, and the median dose reduction dose was 40%. For the 20 patients with dose reduction, the target AUC of 75.000 nM/min was reached: the mean (±SD) observed AUC at cycle 1 was 77.256 ± 8.476 nM/min. Among the 6 patients with initial reduced dose due to impaired renal function, 2 patients required an additional dose reduction (Fig. 1). Among the 12 patients with CrCl ranging between 40 and 60 ml/min, 10 required a diminution of dose, whereas, among the 11 patients with values greater than 80 ml/min, only 2 did. Overall, the mean total dose administered was 6.3 mg/m² (range: 3.1–9.4) and 5.8 mg/m² (range: 2.7–8.9) at cycle 1 and cycle 2, respectively. Among the 33 who received a second cycle, 3 patients required a dose reduction during cycle 2 due to significant decrease of topotecan CL between cycles.

Efficacy

Among the 33 patients who received more than one cycle, 32 patients were evaluable for efficacy. An overall response rate of 19% (based on an intent to treat analysis) was observed, involving one complete response (that lasted 2 months), and six partial responses. Moreover, 10 patients had stable diseases. Among the 12 patients treated in second-line chemotherapy (the first line consisted of paclitaxel-platinum compounds), 4 responses were observed (33%).

DISCUSSION

This study validated major concepts for adapting dosing of topotecan chemotherapy in patients with refractory advanced ovarian cancer. First, an a priori dose adaptation would be recommended according to patient creatinine clearance. Second, individual adaptation of dose occurring at day 4 of treatment, based on drug monitoring performed at day 1, was feasible to reach a target AUC and necessary to reduce the high interpatient variability in topotecan CL, which persists even if variability in renal glomerular filtration rate has been taken into account previously. Finally, we demonstrated that previous lines of chemotherapy, mainly the delay between the last cycle of chemotherapy and the topotecan administration, could also justify a dose adaptation.

Topotecan pharmacokinetics exhibited a large interindividual variability with a coefficient of variation of 40% for CL, as for most anticancer drugs. Total body CL varied by a 10-fold factor. Our study confirmed the relation between topotecan CL and creatinine clearance, already shown by O’Reilly et al. (6). This relation was surprising, because glomerular filtration is a minor pathway of elimination of this drug (topotecan CL largely exceeds 120 ml/min). Because renal CL of topotecan (which
represents around 50% of total CL) also exceeds the glomerular filtration rate, we can conclude that the drug is also eliminated by renal tubular secretion. This was shown by Zamboni et al. (15), who decreased the topotecan renal CL in mice by using probenecid, an inhibitor of tubular transport of anionic compounds. Today, the guidelines for a priori adaptation of topotecan dosage recommend reducing by 50% the administered dose for patients with calculated CrCl ranging between 20 and 40 ml/min, and to exclude patients with lower values. We have followed these recommendations in our study. However, the actual a priori adaptive dosage of topotecan should be reconsidered from our pharmacokinetic-pharmacodynamic results: cutoff of 60 ml/min for CrCl appears more appropriate than the actual value of 40 ml/min because 10 of 12 patients with creatinine clearance in this range required a decrease in dose; 7 of these 12 patients had a DLT. The mean total dose (± 95% confidence interval) administered to these patients was 6.19 (± 0.74) mg/m². For patients with creatinine clearance between 20 and 40 ml/min, the mean dose was 3.55 (± 0.35) mg/m². Then, we recommend a daily dose of 1.2 mg/m², and 0.75 mg/m² for patients with CrCl between 40 and 60 ml/min, and between 20 and 40 ml/min, respectively.

Even if a priori individualization of the initial dose according to the renal status of the patients has been performed, drug monitoring would be necessary to control the overall exposure. Our study demonstrated that this goal is feasible because in most cases, the targeted AUC was obtained (Fig. 2). Indeed, the intrapatient variability in CL within cycles was limited (Table 2). Moreover, by analyzing the data of this study using a population pharmacokinetic approach, we have already devel-

Fig. 1 Relationship between the topotecan CL at day 1 of cycle 1 and the Cockcroft-Gault CrCl for patients with [■] or without [□] dose decrease during cycle 1.

Fig. 2 Ratio between observed total AUC at cycle 1 and AUC predicted according to the topotecan CL at day 1 of cycle 1 for patients with [■] or without [□] dose modification.
Table 3  Number of patients and mean total (i.e., from day 1 to day 5) topotecan AUC at cycle 1 corresponding to each subgroup

<table>
<thead>
<tr>
<th>Mean AUC (±SD)</th>
<th>Without DLT</th>
<th>With DLT</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without dose diminution</td>
<td>(n = 12)</td>
<td>(n = 7)</td>
<td></td>
</tr>
<tr>
<td>64,856 (±14,587)</td>
<td>60,803 (±12,365)</td>
<td>71,803 (±16,398)</td>
<td>0.057</td>
</tr>
<tr>
<td>With dose diminution</td>
<td>(n = 13)</td>
<td>(n = 7)</td>
<td></td>
</tr>
<tr>
<td>77,256 (±8,476)</td>
<td>75,732 (±7,378)</td>
<td>80,086 (±10,210)</td>
<td>0.14</td>
</tr>
<tr>
<td>All patients</td>
<td>68,566 (±12,459)</td>
<td>75,944 (±13,809)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

* One-tailed Student’s t test corresponding to the null hypothesis: AUC is not larger in patients who experienced a DLT.

McGuire et al. (19) However, the value of these efficacy comparisons is limited by the small number of patients included in our study.

The present study is the first integrating the pharmacokinetic-pharmacodynamic relationships previously observed for topotecan. The toxicity results might be considered as a failure because 14 of the 39 patients experienced a DLT, but the reduction obtained in the interindividual variability in AUC allows us to display a potential factor of pharmacodynamic interindividual variability. Clinical studies such as randomized trials are now required to further evaluate the balance between the potential benefits and the logistical obstacles of topotecan drug monitoring.

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REFERENCES


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