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Clinical study

Decreased topotecan platelet toxicity with successive topotecan treatment cycles in advanced ovarian cancer patients

François Goldwasser, Xavier Buthaud, Marine Gross, Pascal Bleuzen, Esteban Cvitkovic, Aline Voinea, Claude Jasmin, Didier Romain[1] and Jean-Louis Misset.
Hôpital Paul Brousse, 12 avenue Paul Vaillant-Couturier, Villejuif 94800 France. [1]SmithKline Beecham Laboratoires Pharmaceutiques, Nanterre 92731, France.

The dose-limiting toxicities of the DNA topoisomerase I inhibitor topotecan are hematological. We prospectively analyzed the platelet toxicity pattern in patients receiving topotecan to optimize the clinical management of topotecan hematotoxicity. Twenty-one advanced ovarian cancer patients, all pretreated with cisplatin and paclitaxel, were treated with 1.25 mg/m^2/day topotecan as a 30 min infusion for 5 days, every 3 weeks. No prophylactic granulocyte colony stimulating factor (G-CSF) was given. No topotecan dose reduction was planned according to hematologic toxicity. One hundred and thirty-three topotecan courses were administered (median per patient 6; range: 1–15). Despite no dose reduction, the mean platelet nadir values were significantly less pronounced at cycle 2 than at cycle 1 (82 versus 46 $\times$ 10^3/mm^3, p=0.0007). Similar differences were found between cycle 1 and any following cycle. The percent of patients experiencing grade 4 thrombocytopenia decreased from 43% at the first cycle, to 15 and 19% at the second and third courses, respectively (p=0.058). We conclude that the currently recommended topotecan schedule is feasible in heavily pretreated ovarian cancer patients without prophylactic G-CSF. The severity of topotecan-induced thrombocytopenia is maximal at the first cycle but significantly decreases from the second cycle in the absence of dose reduction. [© 1999 Lippincott Williams & Wilkins.]

Key words: Ovarian cancer, platelet, topotecan, toxicity.

Introduction

Topotecan (Hycamtin; SmithKline Beecham Pharmaceuticals, Philadelphia, PA), a camptothecin derivative that inhibits the DNA topoisomerase I enzyme,[1] was approved in 1996 for the treatment of ovarian cancer patients following failure of first-line therapy. The dose-limiting toxicity in all phase I studies has been myelosuppression, predominantly neutropenia, and, to a lesser extent, thrombocytopenia.[2] Granulocytopenia was of short duration and non-cumulative. More recently, thrombocytopenia has emerged as a potentially serious clinical problem in heavily pretreated patients.[3] Occult renal impairment may be responsible in part of these observations and an estimation of creatinine clearance is recommended to prevent this risk of life-threatening myelosuppression.[4,5] During the French extended use program of topotecan, we prospectively analyzed the platelet toxicity pattern of topotecan in heavily pretreated ovarian cancer patients.

Patients and methods

Twenty-one recurrent ovarian cancer patients were treated from November 1995 to June 1998 with 1.25 mg/m^2/day topotecan as a 30 min infusion for 5 days, every 3 weeks. The characteristics of the patients are summarized in Table 1. The median time from diagnosis to topotecan treatment was 25 months (range: 8–96 months) and the median of previous chemotherapy regimens was 3 (range: 1–8). All patients were pretreated with cisplatin and paclitaxel. The performance status (PS, ECOG scale) was 2 in 19% of the patients and less than 2 in the other 81%. Median creatinin clearance was 72 ml/min (range: 32–120). Serum bilirubin levels were normal in all the patients. Platelet counts were done twice weekly. Of note, no dose reduction was planned according to either neutrophils or platelet nadir values, even if grade 4 thrombocytopenia, grade 4 neutropenia or

Correspondence to F Goldwasser, Experimental Therapeutics and Translational Research Section, FSMSIT, Hôpital Paul Brousse, 12 avenue Paul Vaillant-Couturier, Villejuif 94800, France.
Tel: (+33) 1 45 59 30 00; Fax: (+33) 1 45 59 35 80;
E-mail: F.Goldwasser@wanadoo.fr

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febrile neutropenia occurred. The only criteria to receive the next topotecan cycle was an increasing neutrophil and platelet count without necessarily full recovery to grade 0, the absence of active infection, and the absence of progressive disease. Observed patient-specific platelet nadirs per course were reported and analyzed. Thrombocytopenia nadirs at each cycle were compared using a non-parametric Wilcoxon matched-pairs test. The percentage of patients experiencing grade 4 thrombocytopenia over cycles was analyzed using a Cochrans Q test.

Table 1. Patient characteristics

Median age (years)	58 (range: 32–73)
Performance status (WHO)	
0	5 (24%)
1	12 (57%)
2	4 (19%)
FIGO stage at diagnosis	
III	16 (80%)
IV	4 (20%)
Patinum resistance status	
sensitive	3 (15%)
resistant	15 (75%)
refractory	2 (10%)
Paclitaxel resistance status	
sensitive	3 (15%)
resistant	15 (75%)
refractory	2 (10%)
Median number of prior chemotherapy regimens	3 (range: 1–8)

Table 2. Patients experiencing grade 4 thrombocytopenia after a cycle of 1.25 mg/m^2/day topotecan daily × 5 every 3 weeks (no dose reduction was done and no granulocyte colony stimulating factor was given)

Cycle 1	9/21 (43%)
Cycle 2	3/20 (15%)
Cycle 3	3/16 (19%)
Cycle 4	2/15 (20%)
Cycle 5	0/12 (0%)
Cycle 6	1/12 (8%)

Table 3. Topotecan-induced thrombocytopenia

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Platelets nadir (10^3/mm^3) (mean)	46	82	84	89	123	82
Platelets nadir (10^3/mm^3) (median)	36	62	79	60	90	84

Results and discussion

A total of 133 courses were administered (median per patient 6; range: 1–15). The mean time interval between two cycles was 22.5 days. Ninety-five percent of the patients experienced grade 3–4 hematotoxicity at the first cycle, the mean number of cycles per patient was 6. No patient discontinued treatment for toxicity. The percent of patients who experienced grade 4 thrombocytopenia significantly decreased with cycles (Table 2) from 43% (nine of 21) at cycle 1 to 15% (three of 20) at cycle 2 and 19% (three of 16) at cycle 3 (p=0.058). Among the nine patients who experienced grade 4 thrombocytopenia at cycle 1, one patient did not receive any other topotecan administration because of progressive disease, two patients experienced again grade 4 thrombocytopenia at cycle 2, three patients experienced grade 3 thrombocytopenia at cycle 2 and three patients had grade 2 thrombocytopenia at cycle 2. Among the 20 patients who received a second course of topotecan, nine (43%) patients improved the grade of platelet toxicity. The mean and median platelet nadir values were significantly less pronounced at cycle 2 than at cycle 1 (82 versus 46 and 62 versus 36, respectively, p=0.0007). Similar differences were found between cycle 1 and any following cycle (Table 3 and Figure 1). The high level of significance tended to decrease with cycles, due to smaller sample sizes. No treatment discontinuation and no dose reduction were done

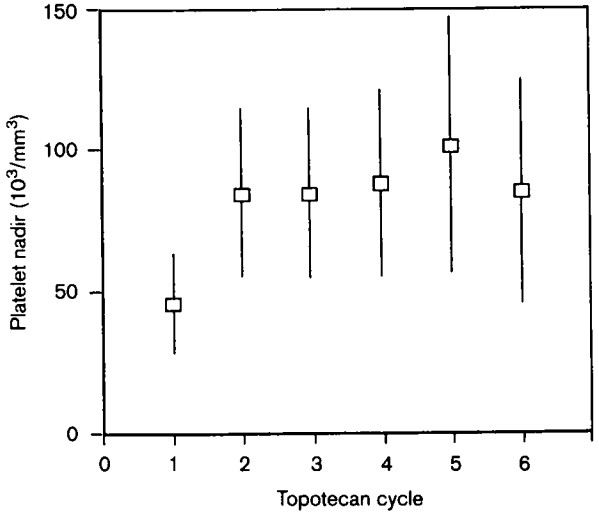

Figure 1. Topotecan-induced thrombocytopenia. Distribution of platelet nadir counts in topotecan-treated patients from cycle 1 to cycle 6. The open squares indicate the mean platelet value and the bars indicate the range of variations within one cycle.

between cycles 1 and 2 to account for the difference. The comparison of renal function between cycle 1 and the following cycles, based on serum creatininemia and estimated creatinin clearance using the Cockroft and Gault formula,[6] did not reveal variations in renal function. Similarly, no change in bilirubin was seen during this period of observation.

The high incidence of severe thrombocytopenia in this population of heavily pretreated patients and the continuation of topotecan treatment at the same dose and interval, whatever the platelet and absolute neutrophil counts both at the nadir and at day 21, allowed the detection of the decrease of severe topotecan platelet toxicity with cycles. No available pharmacokinetic result may account for our observation.[7] In contrast to malignant cells, normal cells have efficient response to DNA damage. Hence, decreased topotecan hematotoxicity with successive administrations might be due to a down-regulation of topoisomerase I expression and/or activity in hematopoietic progenitors.

In conclusion, we show that topotecan platelet toxicity not only lacks a cumulative effect, but is significantly less pronounced from the second topotecan treatment cycle. The median time to objective antitumor response to topotecan is about 9 weeks, longer than with other cytotoxic agents.[4] It emphasizes the clinical relevance of our observation which might reduce the number of patients with suboptimal treatment or untimely treatment discontinuation.

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