Efficacy of Low-Dose Topotecan in Second-Line Treatment for Patients with Epithelial Ovarian Carcinoma

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BACKGROUND. The high incidence of dose-limiting myelosuppresion using the U.S. Food and Drug Administration-approved topotecan dose of 1.5 mg/m^2 for 5 days every 3 weeks may have limited its utility in the treatment of patients with epithelial ovarian carcinoma. The objective of the study was to evaluate the treatment results and toxicity of a low-dose topotecan regimen as second-line treatment for patients with epithelial ovarian carcinoma.

METHODS. A retrospective analysis was conducted of 203 consecutive patients with primary epithelial ovarian carcinoma who were referred to the Finsen Center during the period from June, 1996 to June, 2000. Eligibility criteria included histopathologically documented, International Federation of Gynecology and Obstetrics (FIGO) Stage IC–IV epithelial ovarian carcinoma; first-line treatment with paclitaxel and a platinum compound; and second-line treatment with topotecan (1.0 mg/m^2 intravenously for 5 days every 3 weeks). Efficacy and toxicity were compared with published results from pivotal trials using the approved dose of topotecan of 1.5 mg/m^2 for the same indication.

RESULTS. A total of 56 patients received second-line treatment with the reduced-dose topotecan regimen because of refractory, persistent, or recurrent disease. In the subgroup of patients with platinum-resistant and paclitaxel-resistant disease (n = 43 patients), the response rate of 11.6% (95% confidence interval [95%CI], 3.9–25.1%) was similar to the response rate of 12.4% (95%CI, 6.9–19.9%) in a pivotal trial using standard-dose topotecan. In patients with platinum-resistant and paclitaxel-resistant disease, the median progression free survival and overall survival from the first day of second-line topotecan treatment were 2.7 months (range, 0.7–19.5 months) and 6.0 months (range, 1.0–32.8 months), respectively. In a multivariate Cox analysis, the initial performance status (0 vs. 1–2; P = 0.040; hazard ratio [HR], 2.05) and the performance status at the time of second-line treatment (0 vs. 1–2; $P < 0.001$; HR, 4.50) were identified as independent prognostic factors for overall survival from the start of second-line treatment. Grade 4 neutropenia was noted in only 5.1% of reduced-dose topotecan cycles (95%CI, 2.8–8.4%) compared with 33% and 57% of standard-dose cycles in pivotal studies.

CONCLUSIONS. Topotecan at a dose of 1.0 mg/m^2 has similar efficacy based on response rate and lower toxicity compared with the approved schedule of 1.5 mg/m^2 for 5 days every 3 weeks in second-line treatment for patients with platinum-resistant and paclitaxel-resistant epithelial ovarian carcinoma. However, a comparison of different topotecan doses and schedules preferably should be made in a randomized setting in well-characterized populations with regard to established prognostic factors. ***Cancer* 2002;95:1656–62.**

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Epithelial ovarian carcinoma is a chemosensitive disease with objective response rates of 70–80% after initial cytoreduction and induction chemotherapy with paclitaxel and a platinum compound.[1] Unfortunately, the majority of patients will develop recurrent tumors and die of chemoresistant disease.[1,2] Generally, the treatment of patients with ovarian carcinoma who develop recurrent disease has been guided by the concept of platinum sensitivity.[3] Hence, patients with a platinum free interval in excess of 6 months are considered platinum-sensitive, and most authors favor retreatment with platinum-based therapy.[4–6] Patients with a platinum free interval of less than 6 months usually are considered platinum-resistant, and there is no standard second-line therapy for this patient group.[2]

Currently, three prospective, randomized studies have provided mature results in comparing different drugs for the treatment of patients with platinum-resistant disease; these studies have demonstrating similar activity with topotecan, liposomal doxorubicin, paclitaxel, and paclitaxel-epidoxorubicin with different toxicity profiles for the various regimens.[7–9] The implementation of additional randomized trials are hampered by the fact that the population of patients with platinum-resistant ovarian carcinoma has been used widely in Phase II trials of new agents or older agents in different combinations and schedules because of their general good performance status and reasonable life expectancy.[4] Therefore, retrospective studies on well-defined patient populations with epithelial ovarian carcinoma are valuable to elucidate the effect of the various agents and schedules to be used in forthcoming randomized trials of patients with platinum-resistant ovarian carcinoma.

Most studies of topotecan for the treatment of patients with ovarian carcinoma have used a schedule of 1.5 mg/m^2 for 5 days every 3 weeks intravenously.[10–14] At the Finsen Center, a low-dose regimen of 1.0 mg/m^2 has been applied as standard treatment for patients with platinum-resistant and paclitaxel-resistant ovarian carcinoma since 1997. We performed a retrospective analysis of the efficacy and toxicity of the reduced-dose schedule of topotecan (1.0 mg/m^2 per day for 5 days every 3 weeks) as second-line treatment in patients with epithelial ovarian carcinoma.

MATERIALS AND METHODS

Patients

During the period from June, 1996 to June, 2000, 203 consecutive patients with primary epithelial ovarian carcinoma were treated at our department with paclitaxel and a platinum analogue after they underwent an initial staging operation. Eligibility criteria included 1) histopathologically documented International Federation of Gynecology and Obstetrics (FIGO) Stage IC–IV epithelial ovarian carcinoma; 2) first-line treatment with paclitaxel and a platinum compound after undergoing an initial staging operation; 3) refractory, persistent, or recurrent disease diagnosed by ultrasonography, computed tomography scan, biochemical methods, histology, or a combination of these methods. (For patients with elevated serum CA125 levels and no morphologic evidence of disease, a confirmed rise in serum CA125 level to more than twice the upper limit of normal (< 35 U/mL) was used).[15] 4) second-line treatment consisting of reduced-dose, single-agent topotecan (1.0 mg/m^2 for 5 days every 3 weeks).

Patients were categorized as platinum-sensitive and paclitaxel-sensitive if they had a treatment free interval > 6 months after the end of first-line combination chemotherapy. Patients were considered platinum or paclitaxel-resistant if they had A) progressive disease during first-line combination chemotherapy (refractory disease), B) persistent disease after the end of first-line therapy, or C) responded and subsequently developed recurrent disease within 6 months after the discontinuation of first-line treatment.

Treatment Schedules

Standard first-line therapy consisted of paclitaxel 175 mg/m^2 as a 3-hour infusion followed by a 30-minute infusion of carboplatin at an area under the concentration-time curve (AUC) of 5 repeated every 3 weeks.[16] The glomerular filtration rate was based on ethylenediamine tetraacetic acid clearance. The starting dose of topotecan was 1.0 mg/m^2 per day as a 30-minute infusion given daily for 5 consecutive days and repeated every 3 weeks. Dose alterations were performed according to hematologic nadir and nadir duration. Standard World Health Organization (WHO) toxicity criteria were used. In patients with Grade 4 neutropenia or Grade 3–4 thrombocytopenia, the topotecan dose level was decreased to 0.75 mg/m^2 per day. Dose escalation to 1.5 mg/m^2 per day was performed if Grade ≤ 2 myelotoxicity occurred during the recent treatment cycle. Dose reductions also were prescribed for patients with nonhematologic Grade 3–4 toxicity. Pretreatment laboratory eligibility requirements at the onset of a following cycle were neutrophil count $> 1.0 \times 10^9$/L, leukocyte count $> 3.0 \times 10^9$/L, and platelet count $> 100 \times 10^9$/L; otherwise, the treatment was postponed for 1 week. All patients received standard antiemetic premedication with dopamine antagonists or serotonin antagonists in relation to the treatment.

Duration of treatment was dependent on re-

sponse. All patients were offered at least four courses of topotecan unless disease progression occurred. Chemotherapy generally was continued for two cycles after a complete response was achieved. Thereafter, the patients were followed with monthly serum CA125 measurement and trimonthly clinical examinations for 5 years after their last treatment.

Response Assessment

Response was assessed by routine ultrasonography, clinical examinations, and biochemical methods after every two courses of chemotherapy. All patients had CA125 measurements prior to each cycle. In patients with measurable disease, WHO response criteria were used to verify response. A complete response (CR) was defined as the complete resolution of all tumors and normalization of serum CA125 levels for at least 1 month. A partial response (PR) was defined as a decrease $\geq$ 50% in the product of the greatest dimensions of all measurable lesions. No change (NC) was defined as a bidimensionally measurable decrease $<$ 50% or an increase $<$ 25% in the size of existing lesions. Progressive disease (PD) was defined as an increase $\geq$ 25% in the size of existing lesions or the identification of new lesions.

In patients without measurable disease and with elevated serum CA125 levels, the response criteria reported by Rustin et al. were applied.[17] A response occurred if there was a 50% decrease in serum CA125 levels. Two initial elevated CA125 levels ($>$ 70 U/mL) and a third CA125 level showing a 50% decrease were required to qualify for a response. All complete and partial responses were confirmed by taking a fourth CA125 level at least 28 days after the previous level was determined. PD occurred if there was either a 25% increase in both of two previous CA125 levels, with the increase confirmed by a fourth CA125 level; a 50% increase over three CA125 levels; or persistent elevation $>$ 100 U/mL in the CA125 level for $>$ 2 months without a 50% decrease. NC was obtained if a patient had elevated CA125 levels ($>$ 70 U/mL) and did not qualify for any of the above categories.

The time to disease progression from the start of first-line treatment was defined as the time from the start of first-line combination chemotherapy to the time of the first objective measurement of disease progression. Treatment free interval was defined as the time from the end of first-line therapy to the first day of second-line treatment with topotecan. Progression free survival was defined as the time between the first day of topotecan treatment to the time of the first objective measurement of disease progression or death or the date of analysis (December 1, 2000). Overall survival was calculated from the first day of topotecan treatment to death or the date of analysis.

Statistics

Differences in response rates were compared using a Fisher exact test. Univariate Kaplan–Meyer estimates of overall survival in relation to potential prognostic factors were generated and differences were tested with the log-rank test. The factors were FIGO stage; histology; grade; residual disease after staging operation; initial performance status; response to first-line treatment; treatment free interval from the end of first-line therapy to the first day of second-line treatment with topotecan; age, performance status, number of disease sites and greatest tumor dimension at time of second-line treatment; and response to second-line treatment. The significant factors from the univariate analysis were included in a multivariate Cox regression model to determine the independent prognostic factors for overall survival. The SSPS statistical software package (version 10.0; SSPS, Inc., Chicago, IL) was used. P values $<$ 0.05 were considered statistically significant.

RESULTS

In all, 56 of the initial 203 patients with epithelial ovarian carcinoma received second-line treatment with intravenous topotecan using a reduced dose of 1.0 mg/m^2 for 5 days every 3 weeks as part of an institutional regimen. The patient characteristics are listed in Table 1.

The 56 patients had median 8 cycles (range, 2–14 cycles) of paclitaxel-platinum combination chemotherapy as first-line treatment. The median time to disease progression from the start of first-line chemotherapy for all patients was 8.9 months (range, 1.5–30.8 months; quartiles, 6.2 months and 14.1 months). The patient age at start of second-line treatment was a median of 59.8 years (range, 44.7–77.2 years). All 56 patients had measurable or evaluable disease. None of the patients withdrew from therapy prior to the standard first evaluation after the completion of two topotecan cycles. Patients received a median of 4 cycles of topotecan (range, 2–12 cycles) as salvage therapy. Treatment results in relation to platinum sensitivity are shown in Table 2. The overall response rate for all patients was 17.9% (95%CI, 8.9–30.4%). The response rates for low-dose topotecan for patients with platinum-resistant and paclitaxel-resistant disease and for patients who were platinum-sensitive and paclitaxel-sensitive were 11.6% (95%CI, 3.9–25.1%) and 38.5% (95%CI, 13.9–68.4%), respectively (P = 0.083). In the subgroup of patients with platinum-resistant and paclitaxel-resistant disease (n = 43 patients), the median

TABLE 1
Patient Data (n = 56 patients)

Characteristic	No.	%
FIGO stage		
IIC	1	2
IIIA	2	3
IIIB	5	9
IIIC	33	59
IV	15	27
Tumor grade		
1	2	3
2	15	27
3	21	38
Unknown	18	32
Residual disease after staging operation (cm)		
> 5	34	60
1–5	11	20
< 1	11	20
Performance status at time of second-line treatment		
0	24	43
1	22	39
2	10	18
Platinum-paclitaxel resistant	43	77
Platinum-Paclitaxel sensitive	13	23

FIGO: International Federation of Gynecology and Obstetrics; platinum-paclitaxel resistant: treatment free interval after end of first-line therapy < 6 months; platinum-paclitaxel sensitive: treatment free interval after end of first-line therapy > 6 months.

TABLE 2
Clinical Response in Relation to Platinum-Paclitaxel Sensitivity to Second-Line, Low-Dose Topotecan in Patients with Ovarian Carcinoma who were Pretreated with Paclitaxel and Carboplatin

	Platinum-paclitaxel resistant (n = 43 patients)		Platinum-paclitaxel sensitive (n = 13 patients)		Total patients (n = 56 patients)	
Response	No.	%	No.	%	No.	%
CR	1	2.3	1	7.7	2	3.6
PR	4	9.3	4	30.8	8	14.3
NC	13	30.2	6	46.2	19	33.9
PD	25	58.1	2	15.4	27	48.2
CR and PR	5	11.6	5	38.5	10	17.9

CR: complete response; PR: partial response; NC: no change; PD: progressive disease.

progression free survival and overall survival from the first day of second-line treatment were 2.7 months (range, 0.7–19.5 months) and 6.0 months (range, 1.0–32.8 months), respectively.

In a univariate analysis that included all 56 patients, the following significant prognostic factors for overall survival from first day of second-line treatment were identified: initial performance status (0 vs. 1–2; $P = 0.004$), performance status at the time of second-line treatment (0 vs. 1–2; $P < 0.0001$), and response to second-line treatment (CRs and PRs vs. NC and PD; $P = 0.012$). No prognostic significance for overall survival was found for the following factors: advanced FIGO stage ($P = 0.73$), serous histology ($P = 0.39$), low tumor grade ($P = 0.32$), residual disease measuring > 1 cm in greatest dimension ($P = 0.11$), residual disease measuring > 5 cm in greatest dimension ($P = 0.69$), response to first-line treatment ($P = 0.08$), treatment free interval after the end of first-line treatment (< 6 months vs. > 6 months; $P = 0.078$), age > 60 years at the time of second-line treatment ($P = 0.24$), number of disease sites > 1 ($P = 0.14$), tumor size at the time of second-line treatment > 1 cm ($P = 0.09$), and tumor size at the time of second-line treatment > 5 cm ($P = 0.43$). Independent prognostic factors for overall survival from the start of second-line treatment included only two factors that were identified in a multivariate Cox analysis: initial performance status (0 vs. 1–2; $P = 0.040$; hazard ratio, 2.05; 95%CI, 1.03–4.07) and performance status at the time of second-line treatment (0 vs. 1–2; $P < 0.001$; hazard ratio, 4.50; 95%CI, 1.96–10.35).

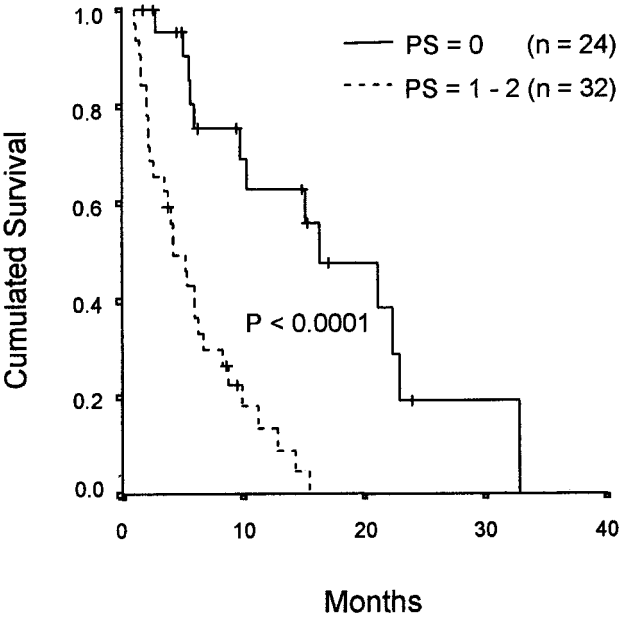

FIGURE 1. Kaplan–Meyer curves of overall survival in relation to performance status (PS) at the time of second-line treatment in patients with epithelial ovarian carcinoma.

Figure 1 shows the overall survival curves regarding performance status at the time of second-line treatment. Fifty percent of patients with a performance status of 0 or a performance status of 1–2 at the

time of second-line therapy expired after 16 months and 4 months from the start of topotecan treatment, respectively. At the time of analysis, 14 patients (25%) were alive with disease, and 42 patients (75%) had died with disease. No patients died of intercurrent disease.

A total of 275 cycles ($n = 56$ patients) were evaluable for toxicity. Failure to achieve hematologic recovery within 28 days and a subsequent delay of 1 week in treatment was noted in 31 cycles (14.1%) because of prolonged neutropenia $< 1.0 \times 10^9$/L (29 cycles) or thrombocytopenia $< 100 \times 10^9$/L (2 cycles). Dose reductions because of Grade 4 neutropenia or Grade 3–4 thrombocytopenia were reported in 5.1% of cycles (95%CI, 2.8–8.4%) and 4.7% of cycles (95%CI, 2.5–7.9%), respectively. One patient (0.4% of total cycles) was referred to hospital and treated with antibiotics intravenously because of fever and infection associated with neutropenia. One patient received platelet infusions because of a bleeding episode and thrombocytopenia. In all, two patients received dose escalations to 1.5 mg/m^2 because of Grade ≤ 2 myelotoxicity in the previous cycle.

Nonmyeloid toxicity generally was mild and was not dose limiting, and the most frequent were nausea, emesis, fatigue, and alopecia. There was no cardiovascular or genitourologic toxicity. Topotecan was abandoned in one patient because of a hypersensitive reaction to topotecan. No patients expired in relation to treatment.

DISCUSSION

In this retrospective review, a low-dose regimen of topotecan (1.0 mg/m^2 intravenously for 5 days every 3 weeks) yielded an overall response rate of 17.9% and a favorable toxicity profile in the second-line treatment of patients with epithelial ovarian carcinoma. In the subgroup of patients with platinum-resistant and paclitaxel-resistant disease (Table 2), it was noted that the reduced-dose regimen used in this study had a response rate (11.6%; 95%CI, 3.9–25.1%) comparable to the response rate of 12.4% (95%CI, 6.9–19.9%) reported in a large prospective study on standard-dose, second-line topotecan (1.5 mg/m^2 for 5 days every 3 weeks) in patients with ovarian carcinoma who were pretreated with a paclitaxel and platinum regimen.[12] A recent study of topotecan at a dose of 1.25 mg/m^2 in patients with surgically documented residual disease after response to first-line therapy with paclitaxel plus carboplatin resulted in a response rate of 31% (95%CI, 16.9–49.3%).[18] However, that study did not include patients like ours with chemorefractory disease.

Comparing the time-to-event parameters in the different trials of topotecan treatment is hampered because of different patient strata. In the current study, the overall survival among patients with platinum-resistant and paclitaxel-resistant disease was a median of 6.0 months (range, 1.0–32.8 months) from first the day of second-line treatment. Bookman et al. found a longer median survival of 11.8 months (range, 0.7–30.5 months) in a comparable group of patients who had received one prior paclitaxel plus platinum regimen,[12] but their results may have been due to the inclusion of patients with potential platinum-sensitive disease. Hence, in the second-line treatment of patients with platinum-resistant and paclitaxel-resistant ovarian carcinoma, a reduced-dose topotecan schedule of 1.0 mg/m^2 appears to have comparable activity based on response rates compared with the approved schedule of 1.5 mg/m^2 for 5 days every 3 weeks; although, obviously, it cannot be excluded that the similarity in response rates may have been due to patient populations with different prognostic factors, thus disguising a true difference in the efficacy of the topotecan regimens.

The limitations of this analysis are acknowledged. It is well established that response rates in retrospective studies tend to be higher than in prospective Phase II and III trials using the same regimen. For that reason, a statistical comparison of the response rates of the low-dose regimen and the U.S. Food and Drug Administration (FDA)-approved topotecan dose of 1.5 mg/m^2 has not been performed. However, the data from this analysis suggest that the dose of topotecan may be reduced without apparent loss of efficacy.

Neutropenia and the subsequent risk for infection and sepsis are the primary side effects in the clinical use of topotecan.[5] In two studies on second-line, standard-dose topotecan treatment, the incidences of Grade 4 neutropenia were 33% and 57% of cycles.[12,19] Using a reduced topotecan dose of 1.0 mg/m^2 for 5 days every 3 weeks, Grade 4 neutropenia was found in only 5.1% of cycles. The incidence of neutropenic fever and infection (0.4% of cycles) with the low-dose regimen was lower compared with the incidence of 4.4% reported by Bookman et al.[12] using standard-dose topotecan. However, an informal comparison of activity and toxicity frequencies in a nonrandomized setting should be made with caution; although the current analysis suggests a more favorable toxicity profile for low-dose topotecan 1.0 mg/m^2 compared with the FDA-approved dose. This finding is interesting, because the recommended topotecan dose of 1.5 mg/m^2 is fairly toxic in the salvage setting.

The 30-minute infusion topotecan schedule over 5 days and repeated every 3 weeks is used widely in clinical practice, although the optimal schedule and administration remain a matter of debate. Preclinical

data on this cycle specific drug suggest that an intermittent schedule over multiple days may be favorable to single-dose therapy.[20] Three Phase I studies showed that a topotecan schedule of 1.5 mg/m^2 intravenously for 5 days every 3 weeks without the use of granulocyte-stimulating factor was the maximum tolerated dose.[21–23] A 3-day dose schedule was evaluated in patients with platinum-resistant and paclitaxel-resistant ovarian carcinoma and showed a limited response rate of 7% (95%CI, 0.8–22.8%) and limited toxicity.[24] This finding is noteworthy, because the 5-day schedule seems to be inconvenient for many patients. A variety of prolonged-infusion topotecan schedules have been evaluated including 24-hour infusions every 3 weeks,[25] 24-hour infusions every week,[13] weekly 72-hour infusions,[26] and a long infusion schedule of 21 days every 4 weeks,[27] but it is uncertain whether a prolonged schedule has an impact on the therapeutic results. Hence, the daily $\times$ 5 infusion schedule remains the standard schedule of topotecan treatment for patients with epithelial ovarian carcinoma.[5] It is noteworthy that a recent randomized study in platinum-pretreated patients examining oral topotecan given on a 5-day schedule demonstrated a response rate (21.4%) similar to the response rate for intravenous administration (21.5%) but with lower toxicity,[19] an observation that warrants further investigation.

The identification of prognostic parameters may lead to grouping of patients that will benefit from targeted therapy.[28] In this study, it was found that performance status at the time of second-line treatment was the most important prognostic factor for survival. Fifty percent of patients with a performance status $>$ 0 at the time of second-line treatment expired after a dismal 4 months from the start of topotecan treatment (Fig. 1). This finding questions the use of second-line chemotherapy in patients with a poor performance status. In this group of patients, the treatment benefit of active chemotherapy must be balanced with its potential toxicity and its inconvenience for patients. The concept of the treatment of patients with recurrent ovarian carcinoma as salvage therapy, in which treatment options must focus on palliation of symptoms and enhancement of quality of life, should be emphasized.

The selection of the optimal treatment strategy for individual patients preferably should be based on results from randomized trials. Currently, three prospective, randomized studies have provided mature results in comparing different agents for the treatment of patients with platinum-resistant ovarian carcinoma.[7–9] Ten Bokkel et al. demonstrated a potential advantage of standard-dose topotecan (1.5 mg/m^2 for 5 days every 3 weeks) compared with paclitaxel (175 mg/m^2 every 3 weeks), as manifested by higher response rates in patients with platinum-resistant disease (13.3% vs. 6.7%, respectively; $P = 0.30$) and a significantly longer overall time to disease progression for all patients (23 weeks vs. 14 weeks, respectively; $P = 0.002$).[7] In a recent, large trial of second-line treatment for patients with ovarian carcinoma, analysis of the subgroup of patients with platinum-resistant disease showed a statistically nonsignificant survival trend in favor of standard-dose topotecan, with a median survival of 9.5 months for patients who received topotecan compared with a median survival of 8.2 months for patients who received pegylated liposomal doxorubicin ($P = 0.455$).[9] However, overall Grade 3–4 hematologic toxicity was more common with topotecan and was more likely to be associated with dose modifications or with the use of growth factors or blood products. A previous randomized study comparing paclitaxel with paclitaxel plus epidoxorubicin in patients with platinum-resistant disease found comparable response rates for the different regimens.[8] The agents that will move toward the next randomized trial will depend on toxicity and feasibility, because all seem to have same response rates in patients with platinum-resistant ovarian carcinoma.[2,4] Furthermore, the route of administration, the presence of prior drug toxicity, and patient preference should be taken into account in the selection of second-line treatment. Nevertheless, currently, single-agent topotecan remains an important second-line choice for the treatment of patients with platinum-resistant epithelial ovarian carcinoma.

In conclusion, the therapeutic index of topotecan may be improved in women with ovarian carcinoma who have disease that is resistant to paclitaxel and platinum using a low-dose regimen of 1.0 mg/m^2 compared with the standard, FDA-approved dose. Hence, a reduced topotecan schedule of 1.0 mg/m^2 for 5 days every 3 weeks should be contemplated if single-agent topotecan is selected in a forthcoming randomized trial of second-line treatment for women with platinum-resistant and paclitaxel-resistant epithelial ovarian carcinoma due to its favorable toxicity profile without apparent loss of activity. Furthermore, to limit overall toxicity, a reduced topotecan dosage should be considered if topotecan is chosen as the second or third component in upcoming trials of new treatment combinations for patients with primary or recurrent disease.

REFERENCES

1. McGuire WP, Ozols RF. Chemotherapy of advanced ovarian cancer [published erratum appears in *Semin Oncol.* 1998; 25(6):707]. *Semin Oncol.* 1998;25:340–308.

2. Deppe G, Baumann P. Advances in ovarian cancer chemotherapy. *Curr Opin Oncol.* 2000;12:481–491.
3. Markman M. "Recurrence within 6 months of platinum therapy:" an adequate definition of "platinum-refractory" ovarian cancer [editorial]? *Gynecol Oncol.* 1998;69:91–92.
4. Ozols RF. Treatment of recurrent ovarian cancer: increasing options—"recurrent" results [editorial]. *J Clin Oncol.* 1997; 15:2177–2180.
5. Herrin VE, Thigpen T. Recent developments in the treatment of recurrent ovarian carcinoma. *Adv Oncol.* 1999;16: 21–29.
6. Gronlund B, Høgdall C, Hansen HH, Engelholm SA. Results of reinduction therapy with paclitaxel and carboplatin in recurrent epithelial ovarian cancer. *Gynecol Oncol.* 2001;83: 128–134.
7. ten Bokkel HW, Gore M, Carmichael J, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol.* 1997;15:2183–2193.
8. Bolis G, Parazzini F, Scarfone G, et al. Paclitaxel vs epidoxorubicin plus paclitaxel as second-line therapy for platinum-refractory and -resistant ovarian cancer. *Gynecol Oncol.* 1999;72:60–64.
9. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized Phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol.* 2001;19:3312–3322.
10. Kudelka AP, Tresukosol D, Edwards CL, et al. Phase II study of intravenous topotecan as a 5-day infusion for refractory epithelial ovarian carcinoma. *J Clin Oncol.* 1996;14:1552–1557.
11. Creemers GJ, Bolis G, Gore M, et al. Topotecan, an active drug in the second-line treatment of epithelial ovarian cancer: results of a large European Phase II study. *J Clin Oncol.* 1996;14:3056–3061.
12. Bookman MA, Malmstrom H, Bolis G, et al. Topotecan for the treatment of advanced epithelial ovarian cancer: an open-label Phase II study in patients treated after prior chemotherapy that contained cisplatin or carboplatin and paclitaxel. *J Clin Oncol.* 1998;16:3345–3352.
13. Hoskins P, Eisenhauer E, Beare S, et al. Randomized Phase II study of two schedules of topotecan in previously treated patients with ovarian cancer: a National Cancer Institute of Canada Clinical Trials Group study. *J Clin Oncol.* 1998;16: 2233–2237.
14. McGuire WP, Blessing JA, Bookman MA, Lentz SS, Dunton CJ. Topotecan has substantial antitumor activity as first-line salvage therapy in platinum-sensitive epithelial ovarian carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 2000;18:1062–1067.
15. Rustin GJ, Nelstrop AE, Tuxen MK, Lambert HE. Defining progression of ovarian carcinoma during follow-up according to CA 125: a North Thames Ovary Group study. *Ann Oncol.* 1996;7:361–364.
16. Neijt JP, Engelholm SA, Tuxen MK, et al. Exploratory Phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. *J Clin Oncol.* 2000; 18:3084–3092.
17. Rustin GJ, Nelstrop AE, McClean P, et al. Defining response of ovarian carcinoma to initial chemotherapy according to serum CA 125. *J Clin Oncol.* 1996;14:1545–1551.
18. Bolis G, Scarfone G, Tateo S, Mangili G, Villa A, Parazzini F. Response and toxicity to topotecan in sensitive ovarian cancer cases with small residual disease after first-line treatment with carboplatinum and paclitaxel. *Gynecol Oncol.* 2001;80:13–15.
19. Gore M, Rustin G, Calvert H, et al. A multicenter, randomised, Phase III study of topotecan (T) administered intravenously or orally for advanced epithelial ovarian carcinoma [abstract 1346]. *Proc Am Soc Clin Oncol.* 1998;17:349a.
20. Houghton PJ, Cheshire PJ, Myers L, Stewart CF, Synold TW, Houghton JA. Evaluation of 9-dimethylaminomethyl-10-hydroxycamptothecin against xenografts derived from adult and childhood solid tumors. *Cancer Chemother Pharmacol.* 1992;31:229–239.
21. Rowinsky EK, Grochow LB, Hendricks CB, et al. Phase I and pharmacologic study of topotecan: a novel topoisomerase I inhibitor. *J Clin Oncol.* 1992;10:647–656.
22. Saltz L, Sirott M, Young C, et al. Phase I clinical and pharmacology study of topotecan given daily for 5 consecutive days to patients with advanced solid tumors, with attempt at dose intensification using recombinant granulocyte colony-stimulating factor. *J Natl Cancer Inst.* 1993;85:1499–1507.
23. Verweij J, Lund B, Beijnen J, et al. Phase I and pharmacokinetics study of topotecan, a new topoisomerase I inhibitor. *Ann Oncol.* 1993;4:673–678.
24. Markman M, Kennedy A, Webster K, Kulp B, Peterson G, Belinson J. Phase II evaluation of topotecan administered on a 3-day schedule in the treatment of platinum- and paclitaxel-refractory ovarian cancer. *Gynecol Oncol.* 2000;79:116–119.
25. Markman M, Blessing JA, DeGeest K, et al. Lack of efficacy of 24-h infusional topotecan in platinum-refractory ovarian cancer: a Gynecologic Oncology Group trial. *Gynecol Oncol.* 1999;75:444–446.
26. Rose PG, Gordon NH, Fusco N, et al. A Phase II and pharmacokinetic study of weekly 72-hour topotecan infusion in patients with platinum-resistant and paclitaxel-resistant ovarian carcinoma. *Gynecol Oncol.* 2000;78:228–234.
27. Hochster H, Wadler S, Runowicz C, et al. Activity and pharmacodynamics of 21-day topotecan infusion in patients with ovarian cancer previously treated with platinum-based chemotherapy. New York Gynecologic Oncology Group. *J Clin Oncol.* 1999;17:2553–2561.
28. Eisenhauer EA, Gore M, Neijt JP. Ovarian cancer: should we be managing patients with good and bad prognostic factors in the same manner? *Ann Oncol.* 1999;10(Suppl 1):S9–S15.