Long-term topotecan therapy in recurrent or persistent ovarian cancer

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Summary

Background: The objective of this study was to evaluate feasibility, safety and clinical outcome of long-term therapy with topotecan (Hycamtin) in recurrent or persistent ovarian cancer. *Patients and Methods:* A retrospective chart review was conducted on all patients treated with topotecan (TPT) at the Department of Obstetrics and Gynecology, University of Bari, Italy between 1999 and 2007. Pertinent clinicopathologic information, response and toxicity following treatment with TPT were collected. TPT was given at a dosage ranging between 1.5 and 1.0 mg/m^2 every three to four weeks. All patients were evaluated for toxicity acording to the CTC and response according to the RECIST response criteria. Time to progression (TTP) was calculated from initiation of TPT treatment and start of the next chemotherapy regimen. *Results:* A total of 30 patients received TPT for at least eight cycles for recurrent ovarian (22), fallopian tube (3) or primary peritoneal carcinoma (5). A total of 432 cycles of chemotherapy were given, with an average of 14.4 cycles per patient (range 8-22). Dose reduction was necessary in 20 patients (66%). About half of the patients required blood transfusions and growth factors. Non hematologic toxicity was mild and manageable. Responses were observed in 16/30 patients (53%), the remaining having SD. Median time to treatment progression was 28 months (range 9-88). *Conclusion:* Long-term treatment with topotecan in recurrent/persistent ovarian cancer is feasible with limited evidence of cumulative toxicity. The results of this retrospective analysis suggest a potential role for late response and survival benefit for those patients without disease progression who continue topotecan therapy beyond six cycles of treatment.

Key words: Recurrent ovarian cancer; Topotecan; Ovarian carcinoma.

Introduction

Ovarian carcinoma is the most common cause of death from gynecologic malignancy in Europe and the United States [1]. Despite high overall response rates to induction platinum and taxane-based chemotherapy, the majority of patients with advanced ovarian cancer will develop recurrent disease within two years, thereafter becoming candidates for further chemotherapy [2].

Several cytotoxic agents have shown good activity in recurrent ovarian cancer, with response rates ranging between 15 and 40%, but none were able to induce durable remission in the absence of continued treatment [3].

A recently published meta-analysis has proved that duration of chemotherapy with topotecan influences survival in recurrent ovarian cancer. In fact, patients who continued chemotherapy for more than six cycles had a statistically significant longer survival (107.0 vs 83.6 weeks) compared to those who stopped treatment after six cycles [4].

The aim of this retrospective study was to evaluate response rate, toxicity and outcome of patients who received long-term treatment (at least 8 cycles) of topotecan for recurrent ovarian carcinoma.

Patients and Methods

The clinical records of all patients treated with topotecan (Hycamtin GlaxoSmithKline, Philadelphia PA) at the Gynecologic Oncology Unit of the Department of Gynecology, Obstetrics and Neonatology (DiGON), University of Bari, Italy between 1999 and 2007 were reviewed. Those patients who received at least eight cycles of chemotherapy were selected and form the basis of our report.

The following data were retrieved from the files of the patients: age, FIGO stage and histology at ovarian cancer diagnosis, previous chemotherapy, details of topotecan treatment (number of cycles, dosages, delays, toxicity, use of growth factors, transfusions, response) and time to treatment progression defined as the interval between initiation of TPT administration and beginning of the following chemotherapy. All patients were staged according to the revised International Federation of Gynecology and Obstetrics (FIGO) staging system [5].

Topotecan was administered intravenously (IV) at a dose of 1.5-1.25 mg/m^2, on days 1-5, as a 1-hour infusion in 250 ml of 5% dextrose. Chemotherapy was repeated every 21 days. In case of severe toxicity (WBC count less than 1,000/µl, platelet count less than 50,000/µl, and organ toxicity), topotecan was reduced to 1.0 mg/m^2 and/or interval between cycles was lengthened to 28 days. Antiemetic medication consisted of ondansetron 8 mg IV plus dexamethazone 20 mg. Patients received G-CSF only in case of grade 4 neutropenia after nadir. Responses were evaluated according to RECIST criteria [6]. In patients who achieved an objective response or disease stabilization after six cycles, therapy was continued until disease progression, and interrupted in case of unacceptable toxicity.

Results

A total of 50 patients were treated with topotecan for their recurrent or persistent ovarian, primary peritoneal and fallopian tube cancer. Of these patients, 30 (22

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Table 1. — *Patient characteristics at the time of ovarian cancer diagnosis*.

Variable	Number or percent	
Age (median)	54 years (range 31-81)	
Stage of disease	I	2 (7%)
	II	4 (13%)
	III	22 (73%)
	IV	2 (7%)
Grading	G1	6 (20%)
	G2	18 (60%)
	G3	6 (20%)
Histology	Serous	18 (60%)
	Endometroid	6 (20%)
	Others	6 (20%)
Previous chemotherapy	Carbo-taxol (1st line)	30 (100%)
	Doxorubicin	9 (33%)
	Taxanes and or platinum	6 (20%)
	Gemcitabine	3 (10%)
	Others	6 (20%)

Table 2. — *Hematologic toxicity according to WHO grade*.

	WHO grade (% of patients)				
	0	1	2	3	4
Leukopenia	40	20	20	20	–
Neutropenia	7	13	37	40	3
Thrombocytopenia	17	43	33	7	–
Anemia	20	7	43	17	13

Table 3. — *Nonhematologic toxicity according to WHO grade*.

	WHO grade (% of patients)				
	0	1	2	3	4
Mucositis	90	10	–	–	–
Nausea/vomiting	7	13	37	43	–
Peripheral neurotoxicity	20	60	13	7	–
Nephrotoxicity	100	–	–	–	–
Alopecia	7	33	40	20	–
Local reactions and phlebitis	90	3	7	–	–

Table 4. — *Response rate according to previous lines of treatment*.

	CR	PR	SD	total
Second-line	2	4	4	10
Third-line	3	4	6	13
More than third-line	1	3	3	7
	6 (20%)	11 (37%)	13 (43%)	30

ovarian, 5 primary peritoneal and 3 fallopian tube carcinomas) were identified as receiving long-term topotecan (at least 8 cycles). Characteristics of these patients at the time of diagnosis are summarized in Table 1. Median age of the patients was 54 years (range 31-81), and most patients had FIGO Stage III, G3 cancers at the time of diagnosis. All had received primary radical surgery followed by first-line chemotherapy with platinum and paclitaxel. A median of 2.1 (range 1-4) previous chemotherapeutic regimens before topotecan treatment had been delivered (one line in 10, two lines in 13 and more than 2 lines in 7). All but six patients (20%) were considered to have platinum-sensitive disease (recurrent disease more than 6 months after completion of first-line chemotherapy).

A total of 432 cycles of topotecan were administered with a median of 11 cycles (range 8-20 cycles). Topotecan cumulative doses ranged from 35 mg/m^2 to 72,5 mg/m^2. All patients were assessable for toxicity. There was no death related to treatment. Grade 3 leukopenia occurred in 20% of patients and grade 3 neutropenia in 40% (Table 2); six patients required G-CSF support for febrile neutropenia. Grade 4 anemia was observed in only three patients and 15 received blood transfusions and erythropoietin (EPO) support during chemotherapy. Nonhematologic toxicity was generally mild; as expected nausea, vomiting, alopecia and neurotoxicity were the most frequent side-effects of the treatment (Table 3). Due to toxicity, six patients (20%) required dose reduction to 1.0 mg/m^2 and in three patients (10%) chemotherapy was administered at 28-day intervals. Furthermore, nonhematologic and hematologic toxicity never caused therapy interruption.

Six patients (20%) had a complete response (CR), 11 (37%) a partial response (PR), and 13 (43%) had disease stabilization (Table 4). The median duration of response in patients with complete response was 38 months. Responses were observed also in third-line and more than third-line chemotherapy. The median time to treatment progression (TTP) for the entire series was 28 months (range 9-88). The PFI was significantly longer for patients who had been only on one prior regimen compared to those who had two or three prior regimens (39.4 vs 18.4 months). There was only one response in the group of patients with platinum-resistent disease.

Discussion

Second- and third-line treatments in patients with recurrent epithelial ovarian cancer provide effective palliation and may extend survival, but relapse is invariable. An effective maintenance therapy that would delay recurrences after a clinical CR or control the progression in partially or minimally responding disease could have a potential impact on survival [7].

The role of consolidation and/or maintenance therapy in ovarian cancer after first-line induction chemotherapy was demonstrated by the Southwest Oncology Group/Gynecologic Oncology Group ((SWOG/GOG) study that showed a 7-month improvement in progression-free survival for patients receiving 12 compared to three cycles of taxolo after complete clinical response [8].

The concept of maintenance after first recurrence is even more compelling as subsequent responses tend to be shorter than the first disease-free interval [9]. However the clinical utility of prolonged maintenance therapy of

patients achieving CR to second-line chemotherapy has not been established [10].

A prescribed number of cycles is reasonable for platinum-based treatment because some long durations of response may be anticipated and continuing beyond six cycles leads to progressive intolerance. Nonplatinum drug regimens, however, should not be subjected to such limitations since they rarely result in CRs, are generally better tolerated, and have no appreciable worsening of toxic effects with repeated cycles [11]. For these reasons maintenance long-term therapy my be an attractive alternative for several second- or third-line drugs as topotecan, caelyx and gemcitabine, that have non-cumulative dose-limiting myelosuppression [3, 4, 9, 10]. Taxanes are also generally well tolerated except for the problematic sensory neuropathy, edema, extensive chronic alopecia and nail changes.

The current experience documents the feasibility of prolonged topotecan therapy in patients who achieve CR, PR or stable disease in recurrent ovarian cancer. In fact, in this study patients tolerated topotecan quite well, with absence of significant cumulative myelosuppression. Non hematologic toxicity was also mild and manageable. Similarily to our study a previous report has documented a limited toxicity (particularly cardiac toxicity) in a group of patients who received one year administration of lyposomal doxorubicin as maintenance treatment for recurrent ovarian cancer [12].

In our study response rate was remarkable even in some cases after the second recurrence or in those patients heavily pretreated. It is, however not possible to state how long treatment should be continued in responding patients.

"Long-term" administration of topotecan is feasible with a moderate toxicity and results in a good response rate both in platinum sensitive and resistant patients with recurrent gynecological cancer.

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