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TOPOTECAN IN THE TREATMENT OF RECURRENT OVARIAN CANCER

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Summary

Topotecan is an efficacious agent in the treatment of ovarian cancer recurrence after the failure of primary chemotherapy with platinum and its derivatives.

Twenty-five patients with recurrent ovarian cancer were treated with topotecan at the Department of Gynecologic Oncology, Clinic for Gynecology and obstetrics, Clinical Hospital Zagreb in the period from January 2004 – January 2005.

All patients were primarily operated and assessed as stage III or IV of ovarian cancer, and therefore received chemotherapy with platinum (in combination with paclitaxel or cyclophosphamide). After their first recurrence in a less than a 6-month interval, topotecan was administered.

A complete clinical response was achieved in 2 patients (8%), a partial response in 15 patients (60%), progression in 8 patients (32%). All patients receiving topotecan were without early reactions (GI- nausea, vomiting), and experienced only mild late reactions (moderate myelosupression).

Eight, 9, 6 and 2 patients received 6, 4, 2 and 1 treatment cycles, respectively.

Based upon the low number of patients included in the study, we may say that topotecan is well tolerated, without significant early and late side-effects and with satisfying treatment response in patients with recurrent ovarian cancer, who are resistant to chemotherapy with platinum.

KEY WORDS: *ovarian cancer, recurrence, topotecan*

TOPOTEKAN U LIJEČENJU RECIDIVA RAKA JAJNIKA

Sažetak

Topotekan je djelotvoran citostatik u liječenju recidiva raka jajnika nakon neuspjeha primarne kemoterapije s platinom i njenim derivatima.

Na Zavodu za ginekološku onkologiju Klinike za ženske bolesti i porode KBC Zagreb u razdoblju od 01/04 – 01/05 liječili smo 25 bolesnica s recidivom raka jajnika topotekanom.

Sve bolesnice su bile primarno operirane i stupnjevane kao III ili IV stadij raka jajnika zbog čega su primale kemoterapiju s platinom (u kombinaciji s paklitakselom ili ciklofosfamidom). Nakon pojave prvog recidiva u vremenu kraćem od 6 mj primjenili smo topotekan.

Kompletni klinički odgovor postigli smo kod 2 bolesnice (8%), djelomični odgovor u 15 bolesnica (60%), progresiju u 8 bolesnica (32%). Sve bolesnice podnijele su primjenu topotekana bez ranih reakcija (GI- mučnine, povraćanje), uz blage kasne reakcije (umjerena mijelosupresija).

Osam bolesnica primilo je 6 ciklusa, 9 je primilo po 4 ciklusa, 6 bolesnica po 2 ciklusa, 2 bolesnice po jedan ciklus.

Zaključak: na osnovi našeg malog broja bolesnica možemo reći da se topotekan dobro podnosi bez značajnijih ranih i kasnih nusdjelovanja uz zadovoljavajući odgovor na liječenje u bolesnica s recidivom jajnika koje su rezistentne na kemoterapiju s platinom.

KLJUČNE RIJEČI: *rak jajnika, recidiv, topotekan*

INTRODUCTION

Ovarian cancer is one of the common tumors of the female reproductive organs and the leading cause of death of all gynecological tumors. The cause of this high death rate lays in the fact that ovarian cancer is usually discovered in its advanced stages (over 75% patients in stages IIb-IV). Early stages are asymptomatic for a long time and are usually discovered by accident.

Surgical procedure (hysterectomy with bilateral adnexectomy with omentectomy and lymphadenectomy) followed by systemic chemotherapy is the usual treatment modality for these patients.

Epithelial ovarian cancers are sensitive to platinum-based cytostatics (cysplatinum, carboplatinum), but a large number of patients who initially showed a good response to chemotherapy will suffer recurrence and die because of resistance to administered cytostatics (1).

Phase II clinical studies of some second-line chemotherapy agents such as: antracyclines, iphosphamide, etoposide gave response in 14-20% of patients with recurrent ovarian cancer. During the mid-1990s, new second-line cytostatics were intensively investigated: paclitaxel, docetaxel, gemcytabin, lyposomal doxorubicin, vinorelbin, topotecan. They all showed a response to treatment in 14-37% of patients resistant to platinum.

Two cytostatics most investigated in monochemotherapy of resistant ovarian cancer are definitely paclitaxel and topotecan.

Thanks to the GOG investigation on a large number of patients, over a thousand, paclitaxel was accepted in 1996 as the treatment of choice in the second line, and in 1998 in combination with carboplatinum in the primary treatment of advanced ovarian cancer (2).

Similar response in the second line of treatment of platinum-resistant ovarian cancer was achieved with topotecan, 14-16% (3).

Topotecan is a semisynthetic water-soluble derivative of camptotecin, inhibitor of topoisomerase I. Topoisomerase I is a nuclear enzyme that enables rotation of DNA thread and restores isolated breakages of DNA during the partition. Camptotecin inhibits the action of topoisomerase

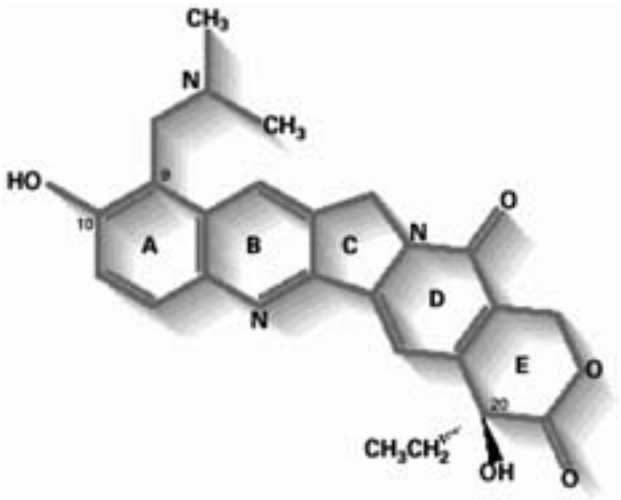


Figure 1. Topotecan structure and characteristics

Name:	Topotecan
Chemical name:	(S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride
Molecular formulation:	$C_{23}H_{23}N_3O_5$ (·HCl)
Molecular weight:	421.453 (free base) 457.91 (as hydrochloride)
Appearance:	Topotecan is a yellow solution
Solubility:	Topotecan is water-soluble

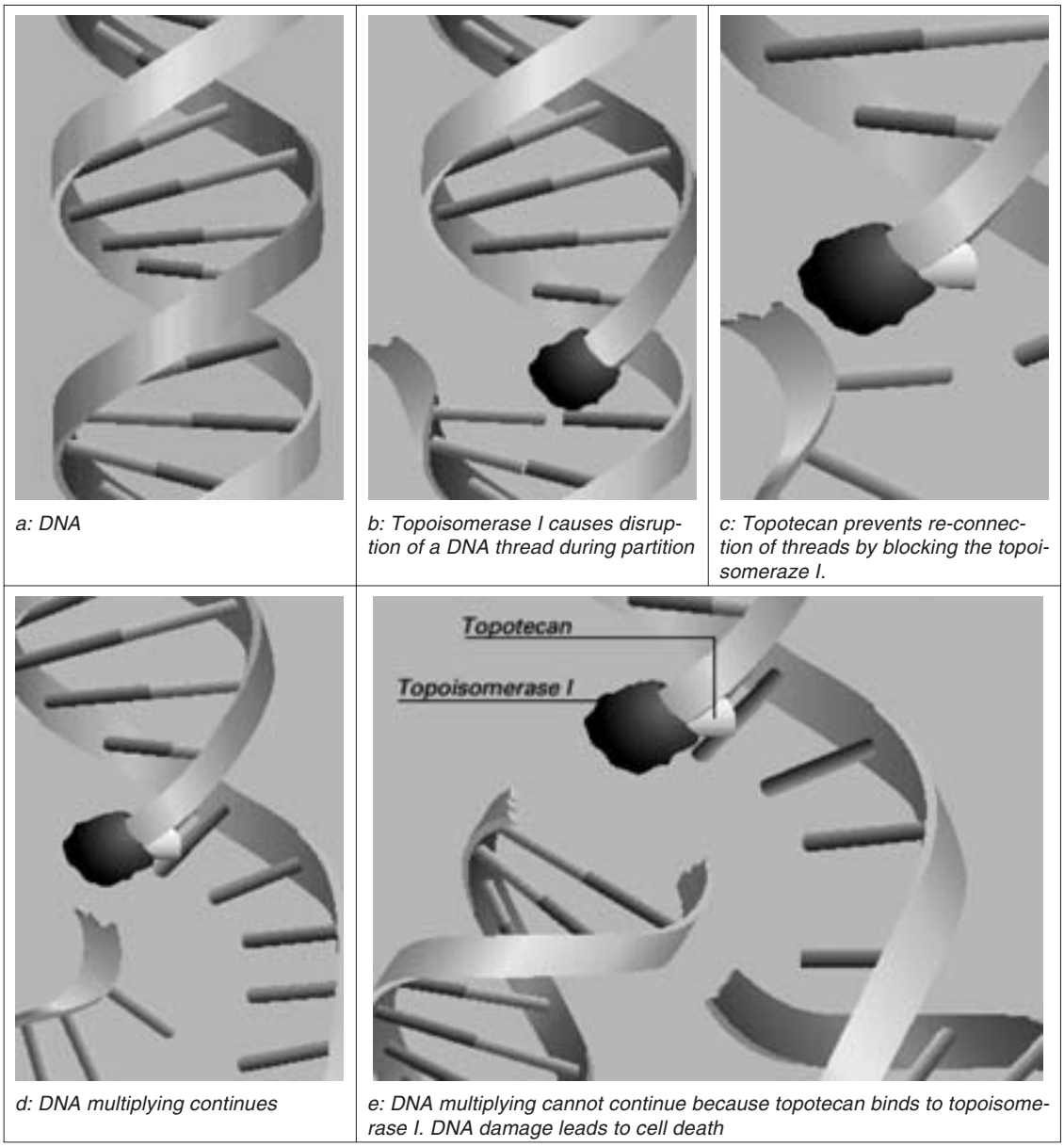
I by creating a covalent bond with the enzyme and disables the reparation of DNA breakages. The accumulation of DNA breakages brings to the cell destruction (4) (Figure 1, Figure 2).

PATIENTS AND METHODS

From January 2004 to January 2005, 25 platinum-resistant patients with ovarian cancer recurrence were treated at the Department of Gynecologic Oncology, Clinic for Gynecology and Obstetrics, Clinical Hospital Zagreb. With primary diagnosis confirmed as epithelial ovarian cancer, they received the first line of chemotherapy with platinum (carboplatinum) and experienced recurrence in less than a 6-month interval.

Treatment

The patients were administered topotecan in a dose of 1.5 mg/m^2 in 1h saline solution infusion for 5 days every 4 weeks.



a: DNA

b: Topoisomerase I causes disruption of a DNA thread during partition

c: Topotecan prevents re-connection of threads by blocking the topoisomeraze I.

d: DNA multiplying continues

e: DNA multiplying cannot continue because topotecan binds to topoisomerase I. DNA damage leads to cell death

Figure 2. Review of the effect of topotecan on DNA

The treatment response was assessed on: clinical examination, gynecologic ultrasound or abdominal ultrasound (depending on the site of the recurrence) and measuring of Ca 125. The assessments were made every 2 cycles.

RESULTS

According to the clinical response assessed by the fall of the tumor marker CA 125 and control US/CT findings, the following results were obtained: 8 of our patients received 6 cycles of chemotherapy with topotecan in a full tumor dose (1.5 mg/m^2 every 4 weeks) of whom 2 (8%) patients had a full clinical response followed by normalization of the tumor marker and normal radiological findings. Six patients (24%) showed a satisfying fall of Ca 125 during the administration of topotecan, but it never reached normal values. The patients felt clinically better, with im-

Table 1.

OVERVIEW OF THE RESPONSE OF THE PATIENTS TO TOPOTECAN TREATMENT

Treatment response	Number of patients (%)	Number of cycles of chemotherapy
Complete response - CR	2 (8%)	6
Stabilization of disease - SD	6 (24%) 9 (36%)	6 4
Progression of disease - PD	6 (24%) 2 (8%)	2 1
Total number of patients	25	

Table 2.

OVERVIEW OF TOXICITY OF TOPOTECAN CHEMOTHERAPY

Toxicity (No. of patients)	Hematological -leukopenia	Non-hematological (GI symptoms)
20 (80%)	15 (75%)	5 (15%)

Table 3.

DEGREES OF HEMATOTOXICITY IN 15 PATIENTS

Hematotoxicity (degree)	Number of patients
G I	5 (33.3%)
G II	8 (53.3%)
G III	2 (13.3%)

provement of radiological findings – disappearance of ascites and reduction of the tumor in the abdomen.

In 9 patients (36%) receiving 4 cycles of chemotherapy, the stabilization of the disease was achieved, but when they were to receive the 5th cycle, there was no further regression because the chemotherapy was discontinued. Considering the fact that the assessments of response to chemotherapy were taken after every 2 cycles, in 6 patients (24%), the deterioration of the disease after the second cycle changed was found and their chemotherapy changed.

Two patients (8%) with poor clinical condition, Karnofsky index under 50%, received only one cycle of chemotherapy because they unfortunately passed away before the next one (Table 1).

During the chemotherapy treatment, special consideration was given to the toxicity associated with the administered medicine, mostly hematological toxicity (leukopenia, trombocytopenia, anemia) and non-hematological toxicity which includes gastrointestinal symptoms, alopecia, neurological damage. Toxicity was found in 20 patients, hematological in 15 (75%), and non-hematological in 5 patients (15%) (Table 2).

Since those were very mild GI symptoms that did not require any treatment, no further assessments were made.

Hematological symptoms were grouped into 3 categories, 2 of which did not require additional treatment except more frequent control of blood count (leukocytes not lower than 1.5, platelets lower than 40, no infections or bleeding). Only 2 patients had significant leukopenia that had to be treated in hospital with granulocyte stimulating factors, fluid restitution and blood derivatives. It must be pointed out that these patients were in poor general condition even before they started chemotherapy (Table 3).

DISCUSSION

Our experiences in the treatment of recurrent ovarian cancer with topotecan have until now been based on literature data only. We did not know how the patients would respond to it, its early and late toxicity or its actual efficiency. Thanks to this small number of patients we can give our own judgment.

During the topotecan administration, no reactions – allergic or GI were found. A few days after the administration, some patients (15%) had mild GI symptoms in the form of nausea, but without vomiting. We administered topotecan in infusion without any premedication – corticosteroids or antiemetics. A week after the chemotherapy, 75% of patients had a drop in their blood count, and 13.3% of whom required both hospitalization and a supportive therapy.

A full response was achieved in 8% of the patients with extension of the free interval up to 6 months, and 60% of the patients had a partial response with a survival rate of up to 4 months. In 24% of patients there was no response to topotecan treatment and they died within 6 to 8 weeks after the conclusion of treatment. Unfortunately, death occurred in 2 patients within 14 days after the administration of the chemotherapy.

In trials with topotecan completed so far, it was shown that in 16.3-38% of patients resistant to platinum treatment response can be achieved,

with remission from 21.7 to 35 weeks. Our patients showed 30% response to topotecan, 8% of which complete remissions in the duration of 6 months and 60% partial responses in the duration of 3 months (5-7).

Ovarian cancer is the leading cause of death in gynecological tumors in developed countries.

This high death rate is mostly due to lack of early symptoms of the disease, so the majority of women present with an advanced stage at the moment of diagnosis. The higher the stage of the disease, the worse the survival rate.

According to FIGO (International Federation of Gynecology and Obstetrics), the 5-year survival rate of stage III patients is 50%, and in the stage IV the survival rate is under 30%.

Although most of the patients responded well to the first line of chemotherapy, the majority of them in the advanced stages experienced reccurrence. An efficient second line chemotherapy that will extend survival and permit people to maintain a good quality of life is still being sought (8).

The usual procedure in epithelial ovarian cancer treatment after the primary cytoreduction is polichemotherapy based upon cysplatinum or carboplatinum in combination with paclitaxel or adriamycine or cycloyphosphamide. Unfortunately, over 70% of patients experience recurrence after their primary treatment. The patients are usually grouped in three groups according to the time of the recurrence as: platinum-sensitive (disease-free interval or period without the signs of the disease >6 months), platinum-resistant (disease-free interval or period without the signs of the disease <6 months) or platinum-refractory (progression or recurrence during the primary chemotherapy). The first group undergoes treatment with the same chemotherapy in case of recurrence, because it is assumed that they are sensitive to it. The other two groups of patients must be treated with cytostatics that do not show cross-resistance, which is topotecan (9-12).

A large number of Phase II trials assessed the efficacy of topotecan as the second line chemotherapy in patients with recurrent ovarian cancer treated with platinum-based chemotherapy. In these trials, the treatment response to topotecan was between 14% and 33%. Total response to topotecan was better in platinum-sensitive patients (19%-33%), compared to platinum-resistant ones (14%-18%). In patients that responded to the treatment with topotecan,the duration of remission was from 4.5 to 11.2 months, with mean survival rate from 6 to 12 months. The use of topotecan until the disease progression was shown to be efficient for survival with acceptable toxicity (Table 4)(13-15).

Phase III clinical trials compared topotecan with paclitaxel, liposomal doxorubicin, oxaliplatinum. In all these trials, topotecan has shown to be almost as efficient as paclitaxel in the second line of chemotherapy. Total response to topotecan was 20.5%, versus 14% to paclitaxel. Mean time to progression for topotecan and paclitaxel was 19 weeks and 14 weeks, respectively . Mean survival was 63 weeks for topotecan, and 53 weeks for paclitaxel. Total response to chemotherapy was 13.1% or 10.2% in patients receiving receiving topotecan or paclitaxel as the third line treatment, respectively. These data show that there is no cross-resistance between paclitaxel and topotecan (Table 5)(16,17).

The results of these trials show that topotecan is as efficient as paclitaxel in the treatment of recurrent ovarian cancer.

Although hematotoxicity of topotecan is higher than that of paclitaxel, there is rarely any significant effect to the efficacy of the treatment or possibility of postponing the chemotherapy.

Table 4.

RESPONSE AND SURVIVAL OF THE PATIENTS TREATED WITH TOPOTECAN

Patients	Earlier chemotherapy (median)	Response	Time to progression (median)	Survival (median)	Author
112	1	20.5%	18.9 weeks	63.0 weeks	Gordon et al.
111	1	16.3%	12.0 weeks	67.9 weeks	Creemers et al.
131	1	19.1%	17.3 weeks	57.6 weeks	Gore et al.
30	1–4 (2)	14.0%	43.2 weeks	10 months	Kudelka et al.
139	1–2	13.7%	12.1 weeks	47.0 weeks	Bookman et al.

Table 5.

RESULTS OF THE SECOND LINE OF TREATMENT WITH TOPOTECAN AND PACLITAXEL DEPENDING ON THE PLATINUM-SENSITIVITY IN EARLIER CHEMOTHERAPY

Platinum-sensitive before the second line	Topotecan					Paclitaxel				
	n	CR	PR	SD	RR	n	CR	PR	SD	RR
Refractory	34	0	3	9	8.8%	33	0	1	10	3.0%
Early recurrence	6	0	1	0	16.7%	10	0	1	4	10.0%
Medium recurrence	20	1	2	6	15.0%	16	0	2	5	12.5%
Late recurrence	52	4	12	17	30.8%	54	3	9	17	22.2%

On the other hand, non-hematological toxicity is very low. There is no proven cumulative neurotoxicity with paclitaxel or cardiotoxicity.

Phase III trials comparing liposomal doxorubicin with topotecan showed that there is no significant difference in total response to treatment, duration of the disease-free interval or survival. Total response to chemotherapy with topotecan was 17%, or 19.7% with liposomal doxorubicin. Duration of the free interval with topotecan was 17 weeks, and 16.1 weeks with liposomal doxorubicin. Survival was 56.7 weeks with topotecan, and 60 weeks with liposomal doxorubicin (18).

In a phase II multicentric randomized trial, oxaliplatinum was compared to topotecan in patients previously treated with platinum. There was no statistical difference found in the treatment response, duration of the free interval or survival.

CONCLUSION

Topotecan has a completely new molecular mechanism of activity and has no proven cross-resistance with other cytostatics. There is only a moderate overlap in hematotoxicity, which has shown as acceptable in trials conducted so far (19).

That leads to the conclusion that topotecan is the cytostatic of choice after the fail of the primary chemotherapy of ovarian cancer with platinum-carboplatinum/paclitaxel.

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