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Topotecan in patients with *BRCA*-associated and sporadic platinum-resistant ovarian, fallopian tube, and primary peritoneal cancers

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Abstract

Objective—To evaluate the efficacy of topoisomerase I inhibitor, topotecan, in patients with recurrent *BRCA*+ versus *BRCA*– ovarian, fallopian tube, and primary peritoneal carcinomas.

Methods—A single-institution retrospective analysis of platinum-resistant patients characterized for the presence or absence of known deleterious *BRCA* mutations. Patients received topotecan at a dose and schedule determined by their treating physician (five day or weekly). Response rate and progression-free survival (PFS) were assessed.

Results—A total of 50 patients (9 *BRCA*+, 41 *BRCA*–) were treated with topotecan. Both groups were well balanced in terms of age, stage, grade, and number of prior therapies. All patients had high-grade serous carcinoma. The clinical benefit rate in *BRCA*+ and *BRCA*– patients was 0% and 26.8% (6 PRs, 6 SDs), respectively ($p = 0.18$). Median PFS in *BRCA*+ and *BRCA*– pts was 1.7 months (95%CI: 1.0 – 2.8mos) and 2.5 months (95%CI: 1.9 - 2.8 mos), respectively ($p = 0.057$). Median time to best response was 1.9 months, and median response duration 2.6 months.

Conclusions—This analysis in a heavily pretreated cohort of patients fails to support the superiority of topotecan in *BRCA*+ platinum-resistant ovarian, fallopian tube, and primary peritoneal cancers. Further study of this class of agents, specifically in less heavily-pretreated patients, may still be warranted.

Keywords

Ovarian cancer; *BRCA*; topoisomerase I inhibitors; topotecan

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INTRODUCTION

Ovarian cancer (OC) is the leading cause of death from gynecologic malignancies in the United States and is the fourth most common cause of cancer death in women.[1] An estimated 21,000 cases are diagnosed in the United States each year, resulting in 15,000 deaths. It is now recognized that approximately 10% of these cases, and 16-21% of the high-grade serous subtype, are due to a hereditary susceptibility, of which *BRCA1* and *BRCA2* mutations account for the majority.[2, 3] Female *BRCA1* and *BRCA2* carriers have a 36-60% and 16-27% lifetime risk of developing OC, respectively.[4, 5] A risk-reducing bilateral salpingo-oophorectomy can significantly reduce, although not entirely eliminate, these risks.[6, 7]

Numerous retrospective and case-controlled studies have reported that patients with *BRCA*-associated (*BRCA+*) OC have better overall survival than patients with sporadic (*BRCA-*) OC.[8, 9] Preclinical data suggest that *BRCA+* OCs are more sensitive to platinum-based chemotherapy.[10] *BRCA+* OCs are now understood to have impaired homologous recombination, the DNA repair pathway responsible for the high-fidelity resolution of platinum-induced double-stranded DNA breaks.[11] One case-control analysis reported higher complete response rates to first, second, and third-line platinum-based chemotherapy in *BRCA+* compared with *BRCA-* OC.[12] Another case series suggested that *BRCA+* OC patients have improved overall survival even when accounting for platinum-sensitivity in a multivariate analysis.[13] These data suggest that both the chemosensitivity and underlying biology of *BRCA+* OC may be more favorable than *BRCA-* OC. Despite these observations, nearly all patients with recurrent *BRCA+* OC will eventually develop platinum resistance and as a result, ultimately die of their disease.

Topotecan is an accepted treatment for platinum-resistant disease, with a historic response rate of 10-15% in several large phase II and phase III studies.[14-16] Topotecan inhibits topoisomerase I leading to stalled replication forks, double-stranded DNA breaks, and irreversible DNA cross-linking.[17, 18] The similarity in DNA-damage caused by topoisomerase I inhibitors and platinum raises the possibility that *BRCA+* OCs may also have increased sensitivity to topotecan. To our knowledge, the activity of topotecan in *BRCA+* versus *BRCA-* OC has never been reported.

We therefore conducted a retrospective analysis of our institutional experience with topotecan in patients characterized for germline *BRCA* mutations. Our objectives were to determine the response rate and progression free survival of topotecan in patients with *BRCA+* versus *BRCA-* OC.

MATERIALS AND METHODS

Patients

Institutional review board approval was obtained for this retrospective analysis. Eligible patients were seen at Memorial Sloan-Kettering Cancer Center (MSKCC) between January 1st, 1995 and February 1st, 2011. Patients were required to have recurrent ovarian, fallopian tube, or primary peritoneal cancer and have had *BRCA* mutation testing on one of two IRB approved research studies. Histologic confirmation of the original primary was required. All patients were platinum resistant according to GOG criteria (platinum-free interval with evidence of progressive disease of < 6 months from last platinum). All patients received topotecan. Patients may have received daily topotecan (Days 1-5, 21-day cycle) or weekly topotecan (Days 1, 8, and 15, 28-day cycle). Patients who received topotecan with an addition cytotoxic, biologic, or hormonal therapy were excluded from analysis.

Tumor Response and Progression Assessment

Responses were determined by clinician adjudicated CT, MRI, or PET scans. The retrospective nature of this cohort precluded use of the Response Evaluation Criteria for Solid Tumors (RECIST) to formally assess these scans. Progression was based on Rustin criteria (CA 125 ≥ 2 x the nadir value)[19], radiologic progression or clinical progression (including death).

Statistical Design

This was a single institutional retrospective analysis with the primary objective of determining the clinical benefit (complete response + partial response + stable disease) rate of topotecan in *BRCA*⁺ and *BRCA*[−] patients. The associations between clinical factors and *BRCA* status/clinical response were tested by either using the Wilcoxon-rank sum test for the continuous variables or the Fisher-exact test for categorical variables. The PFS/OS time is calculated from the therapy starting date to the progression date/the death date/last follow-up date. Univariate PFS analysis/OS analyses were performed stratifying for *BRCA* status. The PFS/OS rate is estimated using Kaplan-Meier method. P-values are obtained by Wilcoxon-Gehan test.

RESULTS

A total of 50 patients were analyzed. Among this group, 9 patients were *BRCA*⁺ and 41 patients were *BRCA*[−]. Baseline demographic data and treatments received are listed in Table 1. There were no major differences between the two cohorts in the distribution of age, histology, grade, pathologic stage, or number of prior therapies. This was a heavily pre-treated cohort with a median of 5 prior therapies (range: 2-9).

Efficacy

Response data by *BRCA* status and treatment received are depicted in Table 2. The clinical benefit rate (complete response + partial response + stable disease) observed in *BRCA*⁺ and *BRCA*[−] patients was 0% and 26.8%, respectively ($p=0.18$). Among the *BRCA*[−] patients, 6 patients had partial responses, and 6 had stable disease. The median time to best response in this group was 1.9 months (range: 0.7 – 4.4 mos), and median response duration 2.6 months (range: 1.1 – 8.3 mos).

Progression-Free and Overall Survival

The median PFS time for the entire 50 patient cohort was 2.4 months (range: 0.66– 11.05 mos). The median PFS in the *BRCA*⁺ and *BRCA*[−] groups was 1.7 months (95% CI: 0.95-2.80) and 2.5 months (95% CI: 1.9-2.8), respectively ($p = 0.057$). The univariate PFS analysis results are listed in Table 3. Of the 50 patients, 39 had died at the time of the analysis. The median OS for the cohort overall was 13.5 months (range: 7.3 – 18.6 mos). The OS of each group by *BRCA* status are listed in Table 4. The median duration of follow-up for the 11 survivors was 7.0 months. The Kaplan-Meier PFS curves for the entire cohort and stratified by *BRCA* status are shown in Figure 1 and Figure 2, respectively. Among responders the median time to best response was 1.9 months (range: 0.7 – 4.4 mos), and the median response duration 2.6 months (range: 1.1 – 8.3 mos).

DISCUSSION

This retrospective analysis did not demonstrate superior activity of the topoisomerase I inhibitor, topotecan, in *BRCA*⁺ compared with *BRCA*[−] OC. In fact, *BRCA*⁺ patients appeared to fair worse both in terms of clinical benefit rate and progression-free survival, although neither difference was statistically significant. This outcome may reflect the

limited number of *BRCA+* patients included in this analysis. It is also possible that the heavily pretreated nature of this cohort obscured differences that would be more apparent in a healthier group of patients. The median PFS for the entire cohort was only 2.4 months, somewhat shorter than would be expected from historical controls. Sehouli et al [15] recently reported a median PFS of 3.7 in 194 platinum-resistant OC patients treated prospectively with one of two topotecan schedules. Those patients had a median of 2 prior therapies, and upfront platinum-refractory disease was excluded. By comparison, the median number of prior therapies in this group was 5, with some patients receiving as many as 9 prior treatments. Unfortunately, germline *BRCA* status of the patients treated in these prospective studies is not available.

Despite the small sample size of this cohort, which precludes any definitive conclusions, these data suggest that it is unlikely that heavily pretreated *BRCA+* platinum-resistant OCs have substantially improved sensitivity to topotecan. The mechanisms by which *BRCA+* and *BRCA-* OCs develop resistance to DNA-damaging agents such as platinum are not well understood. Preclinical data suggest that increased *BRCA1* expression is correlated inversely with platinum sensitivity and that antisense inhibition of *BRCA1* reverses platinum-refractoriness.[10] Other data suggest that *BRCA*-associated OCs may regain functional *BRCA1/2* proteins through a secondary somatic mutation following platinum exposure and that this second mutation confers drug resistance.[20] Similar findings have been observed following treatment of *BRCA*-deficient cell lines with PARP inhibitors, a novel class of anti-neoplastics that specifically exploit tumor deficiency in the homologous recombination DNA-repair pathway.[21] Other data from OC cell lines and mouse models suggest that expression of the drug efflux transporter ABCG2 markedly reduces the protein levels of Top1, the target of topoisomerase inhibitors, and that this results in resistance to the combination of topotecan and olaparib (a PARP inhibitor).[22] Other more traditional mechanisms of acquired drug resistance, such as drug efflux through cellular pumps or secondary non-mutation in non-*BRCA* genes, also likely play important roles in resistance to DNA-damaging agents.

In light of this preclinical data, the disappointing outcomes of the topotecan in *BRCA+* OCs reported here suggest that the mechanisms which confer these tumors with resistance to platinum may also confer resistance to other drug classes that lead to similar double-stranded DNA-breaks. Despite this finding, these two groups of patients appeared to have similar overall survival. It remains unknown whether *BRCA+* OC patients who were less heavily pretreated would benefit disproportionately from treatment with topotecan. . This hypothesis generating exercise suggests that therapies designed to exploit the DNA repair deficiencies of *BRCA+* OCs may best used in less heavily pretreated patients whose tumors have not developed multiple resistant mechanisms.

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Progression Free Survival Curve

Figure 1.

PFS by BRCA Status

Figure 2.

Table 1**Baseline Demographics**

Variables	All	BRCA (-)	BRCA (+)	p-values *
Whole Cohort	50	41	9	
Age at Diagnosis				
Median (Mean)	60(60.04)	62(60.76)	60(56.78)	0.215
Range	40-78	40-78	43-66	
Diagnosis				
Ovarian Ca	46(92%)	37(90.2%)	9(100%)	1.000
Fallopian Tube Ca	3(6%)	3(7.3%)	0(0%)	
Peritoneum Ca NOS	1(2%)	1(2.4%)	0(0%)	
Pathologic Stage (4 missing)				
II	2(4.3%)	1(2.7%)	1(11.1%)	0.333
III	40(87%)	33(89.2%)	7(77.8%)	
IV	4(8.7%)	3(8.1%)	1(11.1%)	
Grade (1 missing)				
G1	0(0%)	0(0%)	0(0%)	1.000
G2	3(6.1%)	3(7.5%)	0(0%)	
G3	46(93.9%)	37(92.5%)	9(100%)	
Number of Previous Therapies (line)				
Median (Mean)	5(4.92)	5(4.76)	5(5.67)	0.223
Range	2-9	2-9	2-9	
Rx				
5-Day Topotecan	8(16%)	7(17.1%)	1(11.1%)	1.000
Weekly Topotecan	42(84%)	34(82.9%)	8(88.9%)	

* p-values for "Age at Diagnosis" and "Number of Previous Therapies" were obtained by Wilcoxon-Rank sum test; other p-values were obtained by Fisher-Exact test.

Table 2

Treatment Outcomes

Variable	Best Response			p-value*
	Pt#	PR/SD	No-response	
All	50	11	39	
BRCA				
(−)	41	11(26.8%)	30(73.2%)	0.177
(+)	9	0(0%)	9(100%)	
Rx				
5-Day Topotecan	8	4(50%)	4(50%)	
Weekly Topotecan	42	7(16.7%)	35(83.3%)	

* p-value was obtained by the Fisher-Exact test.

Table 3

Univariate PFS Analysis

Variable	Pt#	Median PFS Time (Months; 95%CI)	p-value *
All	50	2.4 (1.8-2.6)	
BRCA			
(-)	41	2.5 (1.9-2.8)	0.057
(+)	9	1.7 (1.0-2.8)	

*
p-value was obtained by Wilcoxon-Gehan test.

Table 4

Univariate OS Analysis

Variable	Pt#	Death #	Median OS Time (Months; 95%CI)	p-value*
All	50	39	13.5 (7.3-18.6)	
BRCA				
(-)	41	33	13.5 (7.1-18.3)	0.371
(+)	9	6	18.6 (0.95-Not Estimable)	

*
p-value was obtained by Wicoxon-Gehan test.