

Chemotherapy Toxicity in *BRCA* Mutation Carriers Undergoing First-Line Platinum-Based Chemotherapy

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Epithelial ovarian cancer • *BRCA* mutations • Chemotherapy toxicity • Platinum-based chemotherapy

ABSTRACT

Objective. *BRCA* mutations are the most frequent mutations causing homologous recombination defects in epithelial ovarian cancers (EOC). Germline mutation carriers are heterozygous for the mutation and harbor one defective allele in all cells. This has been hypothesized to cause increased susceptibility to DNA damage in healthy cells as well as neoplastic ones. Our objective was to assess chemotherapy-associated toxicities in patients with epithelial ovarian cancer with and without a germline *BRCA* mutation.

Materials and Methods. A retrospective cohort study of patients with EOC receiving first-line platinum-based chemotherapy at a single center between 2006 and 2016. Indices of chemotoxicity, including blood counts, transfusion requirements, granulocyte colony-stimulating factor (gCSF) prescriptions, episodes of febrile neutropenia, and treatment delays were compared for *BRCA* mutation carriers and noncarriers.

Results. A total of 90 women met the inclusion criteria, including 31 *BRCA* mutation carriers (34%) and 59 noncarriers (66%). Mean hemoglobin, neutrophil count, and platelet counts during treatment were comparable for the two patient groups. There was a trend toward a higher frequency of hematological events in *BRCA* mutation carriers (neutropenia <1500 per mL: 6% vs. 0%, $p = .12$; thrombocytopenia <100,000 per mL: 23% vs. 9%, $p = .07$), but these differences were not statistically significant. Similarly, no significant differences were found in surrogates of bone marrow toxicity such as blood transfusions, use of gCSF, episodes of febrile neutropenia, or treatment delays.

Conclusion. *BRCA* mutation carriers and noncarriers receiving first-line platinum-based chemotherapy for EOC have similar hematologic toxicity profiles. Clinicians treating these patients can be reassured that chemotherapy dosing or schedule do not require adjustment in patients carrying *BRCA* mutations.
The Oncologist 2019;24:e1471–e1475

Implications for Practice: Patients with ovarian cancer carrying *BRCA* mutations are more likely to have serous tumors and present with higher CA125 levels. Germline *BRCA* mutation status is not associated with increased frequency of adverse hematologic events among patients with ovarian cancer being treated with first-line platinum-based chemotherapy. Germline *BRCA* mutations are also not associated with more treatment delays or a lower number of courses completed in this patient population. These findings should reassure practitioners engaged in care for patients with ovarian cancer that *BRCA* mutation status most likely will not affect chemotherapy dosing or schedule.

INTRODUCTION

Epithelial ovarian cancer is the fifth leading cause of cancer-related deaths in women in the U.S. and carries a high case-fatality rate [1]. Patients are commonly diagnosed at an advanced stage and are ubiquitously treated with chemotherapy [2]. Approximately 50% of high-grade serous epithelial ovarian cancers carry a defect in the homologous recombination DNA repair pathway [3]. This is one of the driving mutations in the oncogenetic pathway, but it also

makes these cancers uniquely susceptible to chemotherapy [4–7] and to targeted PARP inhibitors [8–10].

BRCA mutations are the most frequent mutations, causing homologous recombination defects (HRD) in epithelial ovarian cancers [11]. Some of these are purely acquired somatic mutations [12], but a significant proportion of patients have inherited mutations in one allele, rendering them predisposed to the acquisition of a second mutation and the development

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of epithelial ovarian as well as breast cancers [13]. In fact, 15%–20% of patients with high-grade serous epithelial ovarian cancer will be found to carry a germline *BRCA* mutation. In Israel, where a significant proportion of the population is of Ashkenazi or Iraqi Jewish ancestry, the prevalence of germline *BRCA* mutations among patients with epithelial ovarian cancer is nearly 30% [14, 15].

Although in *BRCA*-deficient tumors both *BRCA* alleles are dysfunctional, germline mutation carriers are heterozygous for the mutation and harbor one defective allele in all healthy cells. This is hypothesized to result in lower cellular levels of *BRCA* protein and may lead to a partial HRD and to increased susceptibility to DNA damage, and particularly to double-strand breaks [16]. Such susceptibility in non-neoplastic heterozygous cells may lead to augmented chemotherapy-induced toxicity. Platinum-based chemotherapy, used in first-line treatment of epithelial ovarian cancers, is a powerful inducer of double-stranded DNA breaks [17, 18]. Although increased sensitivity of HRD tumors to chemotherapy has been reported in multiple clinical studies [18–20], reports evaluating chemotoxicity have been few, and their conclusions are inconsistent [21–25].

In light of the sparsity of clinical data on chemotherapy toxicity in *BRCA* mutation carriers, a single institution retrospective cohort study was undertaken exploring differences in chemotherapy-associated toxicities between patients with epithelial ovarian cancer carrying a germline *BRCA* mutation and patients who do not harbor such a mutation.

MATERIAL AND METHODS

This was a retrospective cohort study of consecutive patients with epithelial ovarian cancer receiving first-line platinum-based chemotherapy between 2006 and 2016. Only women tested for germline *BRCA* mutation status were included in the study, and *BRCA* mutation carriers and noncarriers were compared.

The study was conducted according to Good Clinical Practice guidelines and was approved by the institutional review board.

Data Collection

Clinical, pathological, and biochemical data were extracted for each eligible case from patient charts and electronic medical records. Specifically, detailed information regarding the following was abstracted for each cycle of chemotherapy: (a) chemotherapy administration, including date, cycle number, neoadjuvant versus adjuvant, and use of desensitization protocols; (b) hematologic indices including absolute values for complete blood counts (i.e., hemoglobin [g/L], platelet count [K/ μ L], and neutrophil count [K/ μ L]) from a complete blood count collected before initiating each chemotherapy cycle; and (c) other measures of chemotoxicity collected included blood transfusions, use of granulocyte colony-stimulating factors (gCSF), and episodes of febrile neutropenia.

Statistical Analysis

Patients were grouped by *BRCA* mutation status. Baseline clinical and hematologic characteristics were compared for

mutation carriers and noncarriers. Hematologic indices of chemotoxicity, including hemoglobin, platelet, white blood cell, and neutrophil counts were compared for mutation carriers and noncarriers over the course of chemotherapy. Number of cycles received and the mean cycle duration, as a surrogate for treatment delays, were also compared, as were sequelae such as blood transfusions, gCSF prescriptions, and episodes of febrile neutropenia. Comparisons were made using student *t* test for continuous variables, and the chi-square test and Fisher's exact test, as appropriate, for categorical variables. Results were considered significant when the *p* value was no higher than .05. Data are presented as numbers and percentages for categorical variables and means and SD for continuous variables. All statistical analyses were performed on IBM SPSS Statistics for Windows, Version 24.0 (IBM, Armonk, NY).

RESULTS

A total of 210 patients with a new diagnosis of ovarian cancer were treated at Meir Medical Center between 2006 and 2016. A total of 187 patients were diagnosed with high-grade or advanced disease and received at least three cycles of chemotherapy. Eighty-three patients were not tested for *BRCA* mutations. Data were missing for another 14 patients. The study cohort therefore included 90 women who met the inclusion criteria. Of these, 31 were diagnosed as *BRCA* mutation carriers (34%) and 59 were noncarriers (66%).

Table 1 presents the baseline characteristics of the study patients grouped by *BRCA* mutation status. There were no significant differences between the two groups with respect to patient age, disease stage at presentation, or residual tumor at the end of debulking surgery, nor were there differences in the patients' hematological parameters at initiation of treatment. *BRCA* carriers were more likely to have serous tumors (87% vs. 76%, *p* = .009) and had higher CA125 levels at diagnosis (mean, 1710 vs. 791; *p* = .045).

Table 2 presents chemotherapy administration schedule and toxicities in *BRCA* mutation carriers and noncarriers. There were no significance differences between the two patient groups in the total number of courses completed or in treatment delays, as reflected by mean cycle duration.

Mean hemoglobin, white count, neutrophil count, and platelet counts during the course of treatment were comparable for the two groups. There was a trend toward a higher frequency of hematological events requiring treatment delay in *BRCA* mutation carriers (neutropenia <1500 per mL: 6% vs. 0%, *p* = .12; thrombocytopenia <100,000 per mL: 23% vs. 9%, *p* = .07) (Table 3), but these differences were not statistically significant.

There were no statistically significant differences in the frequency of blood transfusions, gCSF administration, or the incidence of febrile neutropenia among *BRCA* mutation carriers and noncarriers (Table 3).

There was also no significant difference in the frequency of hypersensitivity reactions requiring treatment with desensitization protocols between patients carrying *BRCA* mutations and noncarriers.

Table 1. Baseline characteristics of patients with ovarian cancer with and without a *BRCA* mutation

Characteristics	Noncarriers (n = 59)	<i>BRCA</i> mutation carriers (n = 31)	p value ^a
Age at diagnosis, mean (SD), yr	61.3 (±9.9)	61.5 (±10.2)	.91
Histology, n (%)			.009
Serous	45 (76)	26 (87)	
Endometrioid	11 (19)	0 (0)	
Mucinous	2 (3)	0 (0)	
Clear cell	1 (2)	4 (13)	
Stage, n (%)			.16
Missing	3 (5)	1 (3)	
1	7 (12)	1 (3)	
2	8 (14)	1 (3)	
3	34 (58)	20 (64)	
4	7 (12)	8 (26)	
CA-125 at diagnosis, mean (SD), U/mL	791 (±1,727)	1,710 (±2,311)	.04
Neoadjuvant treatment, n (%)	19 (32)	15 (48)	.13
Residual tumor at surgery, n (%)			.73
0 (no macroscopic disease)	30 (64)	11 (50)	
<5mm	13 (28)	9 (41)	
5–10mm	2 (4)	1 (5)	
>10mm	2 (4)	1 (4.5)	
Past malignancy n (%)	5 (8)	3 (10)	.99
Previous chemotherapy n (%)	5 (8)	3 (10)	.99
Hemoglobin, mean (SD), g/dl	11.7 (±1.1)	11.8 (±0.9)	.80
WBC ^b , mean (SD), K/μL	7.0 (±2.4)	6.9 (±2.3)	.89
Neutrophils, mean (SD), K/μL	4.9 (±2.9)	4.9 (±2.1)	.96
Platelets, mean (SD), K/μL	345 (±153)	366 (±149)	.58

^aPearson's chi-square, Fisher exact test, or *t* test as appropriate.^bWhite blood cell count.

DISCUSSION

This study compares measures of hematologic toxicity experienced by patients with ovarian cancer with and without a *BRCA* mutation treated with first-line platinum-based chemotherapy at a single institution.

Despite consistent trends for lower counts in *BRCA* mutation carriers (Table 2), we found no significant differences between *BRCA* mutation carriers and noncarriers in any of the measurable indices of hematologic toxicity (i.e., anemia,

Table 2. Chemotherapy features and hematologic indices in patients with ovarian cancer with and without a *BRCA* mutation

Feature / Index	Noncarriers (n = 59)	<i>BRCA</i> mutation carriers (n = 31)	p value ^a
Cycles completed, mean (SD)	4.9 (±1.7)	5.0 (±1.5)	.68
Cycle duration, mean (SD), wk	3.6 (±0.8)	3.5 (±1.3)	.68
Hemoglobin, mean (SD), g/dL	10.9 (±0.9)	10.8 (±0.9)	.49
WBC, mean (SD), K/μL	5.3 (±1.8)	4.9 (±1.3)	.33
Neutrophils, mean (SD), K/ μL	2.9 (±1.31)	3.1 (±1.1)	.39
Platelets, mean (SD), K/ μL	240.7 (±68.9)	244.4 (±95.7)	.83

^a*t* test.

Note: All hematologic indices reflect complete blood counts taken at the beginning of each chemotherapy cycle.

Abbreviation: WBC, white blood cell.

neutropenia, or thrombocytopenia), nor could we demonstrate significant differences in surrogates of bone marrow toxicity such as blood transfusions, use of *g*CSF, episodes of febrile neutropenia, or treatment delays. Blood counts were usually performed prior to each chemotherapy cycle, and thus, effects on nadir counts remain unknown.

Germline mutations in *BRCA* entail a heterozygous genotype, whereby healthy cells harbor one defective allele; neoplastic cells undergo a second, acquired mutation rendering the second allele dysfunctional. Hypothetically, an inherited mutation could result in the production of lower levels of *BRCA* protein and to an increased susceptibility to DNA damage in heterozygous cells. This is the basis for the hypothesis that mutation carriers may experience more chemotherapy-induced toxicity.

It is also interesting to note that, although not statistically significant, *BRCA* mutation carriers in our cohort tended to present with more advanced disease and received neoadjuvant chemotherapy more frequently. They had higher rates of serous cancers and more elevated CA125 levels, possibly reflecting a higher burden of disease. These features may also contribute to increased chemotherapy toxicity, mediated by functional status.

Only three published studies have investigated chemotherapy toxicity in patients with ovarian cancer carrying a *BRCA* mutation.

A retrospective study of 482 patients with ovarian cancer, including 23 *BRCA* mutation carriers, seen at the Mayo Clinic (Minnesota) between 2000 and 2013, found no increased frequency of adverse events requiring emergency visits or admissions among patients with a family history or those known to carry a *BRCA* mutation [21]. This study included patients with unknown *BRCA* status and did report on detailed hematologic or other toxicities and used emergency department visits and admissions as a surrogate marker.

Another retrospective report on 96 patients with epithelial ovarian cancer in Poland with known *BRCA* status,

Table 3. Frequency of events over the course of first line chemotherapy for patients with ovarian cancer with and without a *BRCA* mutation

Event	Noncarriers (n = 59)	<i>BRCA</i> mutation carriers (n = 31)	p value ^a
Hemoglobin <10 g/DL, n (%)	28 (48)	19 (61)	.24
Hemoglobin <8 g/DL, n (%)	3 (5)	2 (6)	.99
Neutrophils <1.5 K/ μ L, n (%)	0 (0)	2 (6)	.12
Neutrophils <1 K/ μ L, n (%)	0 (0)	1 (3)	.35
Platelets <100 K/ μ L, n (%)	5 (9)	7 (23)	.07
Platelets <75 K/ μ L, n (%)	2 (3)	2 (6)	.61
Blood transfusions, n (%)	14 (24)	6 (19)	.1
Febrile neutropenia, n (%)	7 (12)	2 (6)	.56
gCSF prescribed, n (%)	7 (12)	6 (19)	.34
Hypersensitivity requiring desensitization, n (%)	4 (7)	1 (4)	.99

^aPearson's chi-square or Fisher exact test as appropriate.

Note: All hematological indices reflect complete blood counts taken prior to each chemotherapy cycle.

Abbreviation: gCSF, granulocyte colony-stimulating factor.

including 21 *BRCA1* mutation carriers, indicated that grade 3–4 hematological adverse events were significantly more common among mutation carriers (odds ratio, 3.86; $p = .02$) [25]. Other adverse events, such as neuropathy and GI toxicity, were not increased among mutation carriers. This study included an unselected population with both primary and recurrent disease and a variable number of lines of treatment.

A recent study reported on 432 patients with ovarian cancer receiving first-line treatment at the Princess Margaret Hospital, Toronto, who had undergone genetic testing. The authors found no significant increase across most parameters of hematologic toxicity among *BRCA* mutation carriers compared with noncarriers [16]. There was, however, a statistically significant increase in the frequency of neutropenia grade 3 or higher among *BRCA* mutation carriers.

Some information is also available on chemotherapy toxicity in patients with breast cancer carrying *BRCA* mutations [22–24, 26]. These studies show some mixed results, with one study reporting higher rates of neutropenia in *BRCA* mutation carriers [26]; however, collectively, they support a lack of clinically significant increases in toxicity for *BRCA* carriers in acute hematological events [22], neurotoxicity [24], chemotherapy dosing, or schedule [23].

The major strengths of the current study are the inclusion of a homogenous group of patients with ovarian cancers undergoing first-line chemotherapy in a single institution, as well as the exclusion of patients with unknown *BRCA* status. This is one of few studies evaluating chemotherapy-associated toxicity among patients according to *BRCA* mutation status, and only two others have specifically evaluated patients with ovarian cancer who had undergone genetic testing [16, 25].

Limitations inherent to the retrospective nature of this study included incomplete documentation of patient-reported treatment-induced toxicities in the medical record, including gastrointestinal toxicity, neuropathy, and musculoskeletal toxicity. Another important limitation is the size of our patient population, which may have impacted our ability to make statistically significant observations in light of the small observed differences in the frequency of hematological events. To find significant differences in thrombocytopenia rates such as those demonstrated in our findings, with a power of 80% and a confidence level of 0.95, would have required 250 noncarriers and 85 *BRCA* mutation carriers; sample sizes would have needed to be even larger to demonstrate significant differences in some of the other indices. The small sample size certainly limited the possibility of making any stratifications based on chemotherapy schedule (neoadjuvant vs. adjuvant only, weekly vs. three-weekly) and on patients' history of previous chemotherapy—both important confounders.

CONCLUSION

Despite these limitations, our findings can be interpreted in the context of previous reports on patients with both breast and ovarian cancer, suggesting that germline *BRCA* mutation status is not associated with a significant increase in severe hematologic adverse events among *BRCA* mutation carriers being treated with platinum-based chemotherapy. The trends for higher rates of neutropenia and thrombocytopenia are certainly concerning and warrant increased vigilance for infections and bleeding complications in this patient population. However, these results can collectively be viewed as reassuring, suggesting that *BRCA* mutation status should not have an impact on the choice of chemotherapy dosing and schedule for clinicians treating patients with ovarian cancer.

ACKNOWLEDGMENTS

L.H. is currently affiliated with the Division of Gynecologic Oncology, Juravinski Cancer Center, McMaster University, in Hamilton, Canada.

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DISCLOSURES

The authors indicated no financial relationships.

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