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Comparison of effectiveness of treatment of patients with sporadic and germline *BRCA1*-related ovarian cancer

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ABSTRACT

Objectives: Numerous reports suggest that the clinical course of ovarian cancer (OC) in *BRCA*, including *BRCA1*, mutation carriers (*BRCA1*-OC) is different than in patients with sporadic ovarian cancer (SOC). Most of the authors indicate more favourable treatment results in patients with *BRCA1*-OC. The aim of the study was to compare the effectiveness of treatment of patients with advanced-stage (FIGO III/IV) SOC and *BRCA1*-OC.

Material and methods: Between 2004 and 2009, 957 OC patients were treated in Cracow Branch of Cancer Center, M. Sklodowska-Curie Memorial Institute, Poland. Germline *BRCA1* mutation was found in 66 patients. To compare the effectiveness of treatment, the group of 47 advanced-stage *BRCA1*-OC patients was matched with the group of 47 advanced-stage SOC patients. Pairs of patients were matched in terms of the most important prognostic factors, i.e. stages according to FIGO, primary cytoreduction extent, tumour histologic subtype and grade, as well as year of diagnosis and treatment.

Results: The 5-year overall survival rate was 42.9% for *BRCA1*-OC patients and 34.3% for SOC patients ($p = 0.354$). Mean time to progression was 22.7 and 14.5 months for *BRCA1*-OC and SOC group, respectively ($p = 0.05$). Complete response to primary surgery and first line chemotherapy was obtained in 42.5% and 37.9% of cases, respectively; the difference, however, did not reach the statistical significance.

Conclusions: Results of combined treatment in the group of *BRCA1*-related OC patients seem to be better than in the group of sporadic ovarian cancer patients.

Key words: ovarian cancer, *BRCA1*, chemotherapy, cytoreduction

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INTRODUCTION

Numerous reports suggest that the clinical course of OC in *BRCA1/2* mutation carriers is different than in women with sporadic OC. Most of the authors indicate more favourable treatment results in *BRCA1/2*-related ovarian cancer patients; the data, however, were obtained predominantly in the American, British and Jewish population [1–5]. It is considered that due to the mutation of *BRCA1* and *BRCA2*, resulting in DNA repair impairment, *BRCA*-related cancers are more sensitive to cytostatic agents that induce double strand DNA breaks, such as cisplatin and carboplatin [6, 7]. Only few authors single out *BRCA1*-OC subgroup from the entire *BRCA1/2*-OC group. Additionally, literature reports do not distinguish the advanced-stage (FIGO III/IV) patient group. Moreover, except for one paper on 18 *BRCA1* mutation carriers, there are no reports on Polish women [8]. It seems that genetic differences might induce a different clinical course of OC in the Central-European population.

Data presented in the literature are retrospective and compare groups of different number of patient and, sometimes, of non-uniform distribution of demographic, histopathological and clinical features.

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AIM OF THE STUDY

The aim of the study was to compare the effectiveness of treatment of patients with advanced-stage SOC and *BRCA1*-OC.

MATERIAL AND METHODS

The report presents the analysis of clinical data including 957 patients with OC treated in Cancer Center, M. Sklodowska-Curie Memorial Institute, Cracow Branch between 2004 and 2009. Based on the family history of hereditary breast and ovarian cancer, the group of 249 patients was identified. Blood samples were taken from patients, after obtaining their written consent, to perform genetic testing for germ-line *BRCA1* mutation carrier state. Exons 2, 5, 11 and 20 of *BRCA1* were examined. The material was screened for *BRCA1* mutations, which are the most frequent in the Polish population, i.e. 4153delA, 5382insC C61G, 185delAG, and 3819del5. Genetic testing was performed using denaturing high-performance liquid chromatography (dHPLC), restriction fragment length polymorphism analysis (RFLP) and DNA sequencing, 47 patients with advanced-stage *BRCA1*-OC were selected from 66 *BRCA1* carriers and matched with 47 SOC patients. Demographic, histopathological and clinical characteristics of the studied groups were determined by pair matching in terms of primary prognostic factors including cytoreduction extent, histologic subtype (serous vs. non-serous cancers) and tumour histologic grade G. The aim of matching was to eliminate, as much as possible, the influence of other factors than *BRCA1* mutation that might affect the outcome of the treatment.

The response to combined treatment (surgery + chemotherapy) was evaluated based on the medical examination, imaging (RECIST 1.0 criteria) and marker assay (CA125 marker level in blood serum) as well as second-look surgery. All the patients were followed up for at least 3 years, unless a patient died within that period.

The effectiveness of treatment was evaluated according to the time to progression, defined as the period between the start of treatment (date of surgery or first cycle of induction chemotherapy) and cancer recurrence confirmed by medical or imaging examination, and the overall 5-year survival rate calculated from the date of start of treatment. The mean follow-up time was 65 months. The survival probability was estimated using the Kaplan-Meier method [9]. The Peto log-rank test was used to evaluate the statistical significance of differences in observed results [10]. The statistical significance level was set at $p \leq 0.05$.

RESULTS

Demographic, histopathological and clinical characteristics of the group of 47 pairs of patients with advanced *BRCA1*-OC and SOC are presented in Table 1.

Patients with menopause constituted 55.3% of both *BRCA1*-OC and SOC groups. The mean age of patients was 48.2 and 54.2 years, respectively. The optimal cytoreduction (defined as residual disease < 1 cm) was obtained in 21 (44.7%) patients in each of the groups. In accordance with the international recommendations, all the patients were given platinum-based chemotherapy. Paclitaxel + platinum regimen, considered currently to be the "gold standard" for OC adjuvant treatment, was applied in 33 (70.2%) and 31 (65.9%) cases, respectively. No statistically significant differences were observed between the two groups in regard to applied chemotherapy regimens.

The 5-year survival rate was 42.9% for *BRCA1*-OC patients and 34.39% for SOC patients. The difference in the survival rate was not statistically significant ($p = 0.354$). Predicted overall survival rates for both groups are presented in Figure 1.

Table 1. Demographic, histopathological and clinical characteristics in the group of 47 patient pairs with advanced *BRCA1*-OC and SOC

Demographic, histopathological and clinical characteristics	Patients with *BRCA1*-OC n = 47	Patients with SOC n = 47	P value
Patient age			
< 50 years	18 (38.3%)	19 (40.4%)	
> 50 years	29 (61.7%)	28 (59.6%)	0.833
Menopause			
Yes	26 (55.3%)	26 (55.3%)	
No	21 (44.7%)	21 (44.7%)	1
Body mass index			
< 25	24 (51.1%)	27 (57.4%)	
25–30	16 (34%)	15 (31.9%)	
> 30	7 (14.9%)	7 (14.9%)	0.763
***BRCA1* mutation type**			
5382insC	16 (34%)	–	
189delAG	2 (4.3%)		
C61G	27 (57.4%)		
Other	2 (4.3%)		n/a
Coexisting breast cancer	6 (12.8%)	0	0.011
Tumour histologic grade			
G1	2 (4.2%)	1 (2.1%)	
G2	13 (27.7%)	14 (29.8%)	
G3	32 (68.1%)	32 (68.1%)	0.831
Cancer histologic subtype			
Serous	21 (44.7%)	21 (44.7%)	
Endometrioid	11 (23.4%)	11 (23.4%)	
Mucinous	8 (17%)	8 (17%)	
Other	7 (14.9%)	8 (17%)	1
Cytoreduction extent			
Optimal	21 (44.7%)	21 (44.7%)	

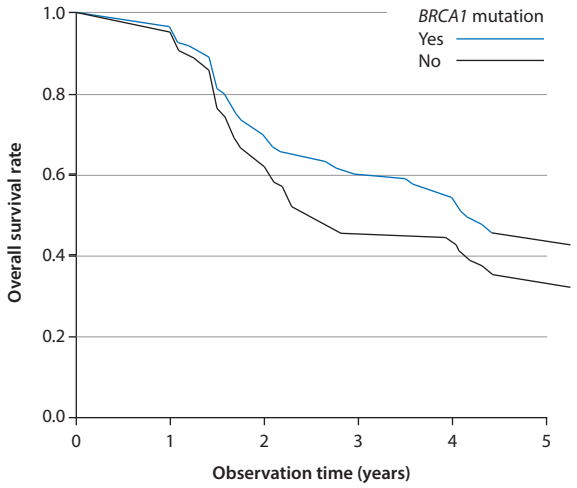

Figure 1. Cumulative survival rate of patients with advanced OC according to *BRCA1* mutation carrier state

Table 2. Treatment outcome of *BRCA1*-OC and SOC patients

Parameter	*BRCA1*-OC n = 47	Sporadic OC n = 47	P value
5-year overall survival rate	42.90%	34.30%	0.35
Median survival time (months)	49	48	0.09
Mean time to progression (months)	**22.7**	**14.5**	**0.05**
Treatment response — CR (complete response)	20 (42.50%)	15 (31.90%)	0.28

Table 2 presents treatment outcome comparison between both groups of patients in regard to the 5-year survival rate, median survival time, time to progression and response to combined treatment.

In 38 women with *BRCA1*-OC, disease progression was observed within the abdominal cavity and, in 3 cases, also within the pleural cavity. In the SOC group, disease recurrence was observed in 40 patients; it was located within the abdominal cavity and, in 4 cases, also within the pleural cavity. The recurrence rate for patients with complete remission of the examined *BRCA1*-OC and SOC groups (20 and 15 women, respectively) was 75% and 66%, respectively.

DISCUSSION

The presented report is the analysis of the biggest, so far, group of East Central European patients with *BRCA1*-OC. In the literature, there are no prospective studies comparing treatment outcome of *BRCA1*-OC and SOC patients; additionally, available data do not focus on the advanced-stage OC, but also include early-stage cases of a definitely more favourable prognosis.

Tan et al. in their report from 2008, matched 1:2 22 *BRCA1/2*-OC patients with 44 SOC women for FIGO stage, histologic subtype, and age in the year of diagnosis [1]. They showed statistically significant differences in the response to the second and third line platinum-based chemotherapy, longer treatment free interval (TFI) between subsequent chemotherapy cycles, and higher 5-year overall survival rates in patients with *BRCA1/2*-OC compared to SOC patients. More importantly, the authors showed that there were no differences in the response to non-platinum agents in any of the 3 chemotherapy cycles. However, the analysis was based on a small number of patients. Results of no statistical doubt were reported by Zweemer et al. in 2001, who compared the group of 44 *BRCA1/2*-OC patients with the group of matched 176 SOC cases. The difference in median survival was 21.5 months and in the 5-year survival rate was 6,1% in favour of patients with *BRCA1*-OC [3].

In this report, as compared to the literature data, pair matching criteria were extended to include cytoreduction extent (optimal < 1 cm or sub-optimal ≥ 1 cm) and tumour histologic grade so as to eliminate other significant prognostic factors that might influence the outcome of the treatment. The distribution of applied adjuvant chemotherapy regimens (platinum-based agent + paclitaxel and platinum-based agent + another cytostatic) was also similar in both groups. The obtained outcome of the treatment, however, is ambiguous due to the lack of statistical significance of the majority of the results; however, a distinct trend suggesting more favourable prognosis for *BRCA1*-OC patients has been observed. Only time to progression proved to be statistically longer by 8.2 months in *BRCA1*-OC patients (22.7 months *vs.* 14.5 months, $p < 0.05$). The number of cases without complete remission after combined therapy was lower in the group of *BRCA1*-OC patients than in the SOC group, 27 (67.5%) *vs.* 32 (76.2%) cases, respectively, which might indicate a better response to platinum-based chemotherapy and is consistent with literature reports [11–14].

A better response to chemotherapy in terms of complete remission rate in *BRCA1*-OC patients as compared to SOC patients was also observed by Cass et al., Majdak et al. in turn reported lower, compared to this report, complete pathological remission in women with *BRCA1*-OC. No differences in response to chemotherapy was also observed in a large Norwegian follow-up study [8, 11, 15].

Results of the discussed studies were mostly based on the Jewish, American and British, or Scandinavian population data. The literature lacks reports on patients of East Central Europe origin, different in genetic regard as mentioned before. The only report on the outcome of the treatment in Polish *BRCA1*-OC patients was presented in 2005 by Majdak et al.; however, it included only 18 cases [8].

Results presented in the report should be analysed, taking into account limitations of the study material. Firstly, the retrospective character of the data does not allow to draw general conclusions and generates limitations regarding data accuracy. Secondly, the number of patients in both groups is limited, which does not allow to reach, for example, statistical significance of overall 5-year survival rate in spite of the evident difference in Kaplan-Meier curves. Thirdly, a part of the group was treated using older chemotherapy regimens without taxanes. Fourthly, the group of *BRCA1*-OC patients included 6 (12.8%) cases with earlier breast cancer, which might had worsened the prognosis. And finally, a relatively small percentage of patients had complete remission after combined treatment, which might be due to the high rate of second-look surgeries (14.9% in total) confirming residual microscopic disease or due to too optimistic description of the debulking that is widely discussed in the literature regarding extent of surgical treatment in OC [16].

CONCLUSIONS

To conclude, the differences in the treatment outcome between two analysed groups of patients are ambiguous. The only parameter of statistical significance ($p = 0.05$) suggesting more favourable treatment outcome in advanced-stage *BRCA1*-OC patients was mean time to progression. Other parameters proved no statistical significance in spite of a distinct trend toward better treatment outcome in the group of *BRCA1*-OC patients.

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