SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Investigation of the prognostic value of poly (adenosine diphosphate ribose) polymerase expression in epithelial ovarian cancer

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The PhD defense will be held on 16 November, 2021. at 1 p.m.

Live online access will be provided via Webex. If you wish to join the discussion, please send an e-mail to the molnar.szabolcs@med.unideb.hu address until 12 p.m. at latest on the previous day of the defense (November 15, 2021). For technical reasons, after the deadline, it will not possible to join the defense.

1. INTRODUCTION AND AIMS

Ovarian cancer is the third most common gynecological tumor after malignancies of the cervix and uterus. It is the seventh most common cancer among women and the eighth most common cause of cancer deaths. Over the last 30 years, the number of newly identified cases has shown a steady increase. The disease is recognized in advanced stage in more than two-thirds of cases.

Treatment of the disease has been based on cytoreductive surgery and platinum-based chemotherapy for decades. During surgical care, the goal always is the complete removal of the tumor; the intervention is considered optimal if no visible tumor remains in the abdominal cavity. The amount of tumor remaining after surgery is closely correlated with the prognosis of the disease, so it can be considered one of the most important prognostic factors. Another pivotal point in the treatment of the disease is platinum based systemic therapy. In addition to optimal tumor reduction, response to platinum-based chemotherapy is considered to be the other major prognostic factor for disease outcome. The response to therapy is measured by the length of the progression-free interval after the end of treatment, the longer this period, the more favorable the long-term outcome. Patients with a progression-free interval of more than 12 months are considered platinum-sensitive. We do not currently have reliable markers to predict or estimate the tumor response to platinum-based treatment.

The effect of classical antitumor drugs is based on the destruction of the chromosomal integrity of the cells, which in most cases is achieved by inducing DNA

damage, thereby reducing the survival capacity of the tumor cells. However, the DNA damaging effects of cytotoxic agents may be offset by properly functioning DNA repair mechanisms in cells. The PARP enzyme is responsible for regulating an alternative DNA repair pathway, and its role is essential in recognizing breaks affecting only one strand of DNA and initiating the repair process. Inhibition of the PARP enzyme is one of the latest therapeutic options in the treatment of ovarian cancer. In patients where the homologous DNA repair pathway of tumor cells is impaired, inhibition of PARP can accumulate a degree of DNA defect in tumor cells that leads to cell death. Theoretically, overexpression of the PARP enzyme in tumor cells may lead to an increase in DNA repair capacity, which may lead to a reduced efficacy of chemotherapeutic drugs. Increased PARP expression in tumor cells may therefore be a good marker of reduced susceptibility to DNA-damaging environmental effects, such as platinum-based chemotherapeutic agents commonly used in the treatment of ovarian cancer.

The primary goal of our studies was to investigate the PARP expression of tumor cells and its relationship to tumor platinum sensitivity. A secondary objective of our studies was to investigate the prognostic value of the PARP immunohistochemistry in BRCA mutation-carriers and BRCA wild-type patients.

In our research, we primarily aimed to identify clinically applicable molecular markers that can more accurately predict prognosis, expected chemotherapy response, progression-free period and relapse, and may assist in the development of more optimal treatment strategies for ovarian cancer patients in the future.

2. MATERIALS AND METHODS

2.1. Patient population

Patients diagnosed with HGSOC between 2011 and 2019 at the Department of Obstetrics and Gynecology of the University of Debrecen were included in our retrospective cohort studies. All patients enrolled underwent complete oncology treatment consisting of primary cytoreductive surgery as recommended by the current European Society of Gynecological Oncology (ESGO) and adjuvant platinum-based chemotherapy. In our own practice, we use a combination of paclitaxel and carboplatin in 6 cycles in 3-week cycles (Q3W). All patients were required to undergo follow-up visits every 3 months, which consisted of a physical examination and performance status assessment, with monitoring of ovarian specific tumor markers (Ca 125 and HE4). In case of clinical suspicion of recurrence or increase in tumor marker values, recurrence was confirmed in all cases by imaging.

2.2. Methods

2.2.1. PARP immunohistochemistry

We collected archived tissue samples of ovarian cancer at the Department of Pathology, University of Debrecen. We performed histology and immunohistochemistry tests, according to the standard operating procedures of our diagnostic laboratory. Tissue samples were fixed with formaldehyde (4% in phosphate buffer saline) for 24h. The protocol of dehydration and paraffin embedding followed the standard operating procedure. Tissue blocks containing representative tumor tissue were selected and cut

to obtain 4 µm thick sections. Every evaluated tumor sample stemmed from the primary tumor tissue. Immunostaining to highlight PARP protein expression was performed using a Leica Bond MAX Immunostainer (Leica Microsystems, Wetzlar, Germany). For immunostaining, we used a rabbit polyclonal anti-PARP antibody (ab6079 330, Abcam, Cambridge, UK). Tissue sections were deparaffinized and subjected to heat-induced epitope retrieval for 10 min at pH 9.0. The primary antibody was optimal at 1:500, using the Bond Refine- HRP detection system (DS9800, Leica Microsystems, Wetzlar, Germany). We assessed the intensity and the distribution of immunostaining by light microscopy (Leica DM2500 microscope, DFC 420 camera, and Leica Application Suite V3 software; Leica). The intensity of specific immunolabeling was determined using a four-grade (0–3+) system, where "0" was equivalent to the complete lack of staining and "3+" represented stable and uniform nuclear positivity in the tumor cells. We gave a "2+" score in cases of clear positivity appearing weaker than the maximal intensity. In contrast, "1+" staining included weak and sometimes highly variable nuclear staining, which was generally different from "0" score. Attempting to define the frequency (%) of positive nuclei failed due to the heterogeneous composition of the tumor tissues. While in most cases with a solid tumor, the fluctuation in staining (virtually 100%) could not be presented, a significant portion of samples included large non-neoplastic areas (stromal component, inflammation, severe fibrosis) intermixed with the tumor. IHC and their evaluation were performed in collaboration with the Institute of Pathology, University of Debrecen (ETT 60355–2 / 2016 / EKU).

Before the final analysis, the study population was dichotomized into subgroups: “any” or “no” PARP expression. The PARP positive group was created from samples, where at least weak staining (1+) was observed in more than 10% of tumor cells. Our hypothesis was that this PARP positive cell population may be sufficient to serve as a starting point for early relapse based on PARP-induced platinum resistance.

2.1.2. Examination of BRCA status

Every included patient had known BRCA status. Somatic BRCA1 or BRCA2 mutation carriers were identified with bidirectional sequencing of DNA from archived tumor tissue. If the test could not be performed due to technical reasons, the sequencing was done from peripheral blood cells to identify germline mutation carriers.

2.3. Data collection and statistical analysis

Clinicopathological features of the cases were analyzed. The primary endpoint was the progression-free interval between the date of the last chemotherapy cycle to the date of radiologically confirmed relapse. The secondary endpoint was the overall survival (OS) at the final analysis to the dichotomized population, and the results were stratified by BRCA status. We calculated descriptive statistics, including the means, medians, and proportions. We used Student’s *t*-test or the Mann–Whitney test and the chi-square test or Fisher’s exact test for the statistical comparisons of continuous or categorical variables, respectively. We generated survival curves using the Kaplan–Meier method and performed Cox proportional hazard regression to identify prognostic

variables for progression-free survival (PFS) and for overall survival (OS). We used SPSS version 21.0 (IBM Corporation, Armonk, NY, USA) for statistical calculations, with significance set at $p = 0.05$ and power set at a level of 80%. The odds ratio (OR) and 95% confidence interval were calculated to predict the effect of PARP positivity on relapse, the PFS less than 12 months, risk of death, and survival shorter than 32 months. Using OR calculation, the PFS was limited to 12 months because this period of platinum sensitivity is determined by definition. Based on the OS the end value was 32 months or less. In our second study, we also analyzed these odds ratios for BRCA status. For the calculation of the odds ratio, the cut-off value for PFS was set at 12 months, as this can also be considered as the limit of platinum sensitivity.

3. RESULTS

3.1. Investigation of the prognostic significance of PARP expression in high-grade epithelial ovarian cancer patients

In our first study, we examined the prognostic significance of PARP expression as a function of clinical characteristics in patients with high grade epithelial ovarian carcinoma. In our database, 86 patients met our inclusion criteria, and none of the patients received chemotherapy prior to performing PARP IHC. The mean age of the patients was 57.23 ± 11.13 years. 81.39% of patients were diagnosed at an advanced stage (FIGO IIIB-IV). During primary debulking surgery, 50% (n = 43) of the patients achieved macroscopically tumor-free status. The median follow-up was 32.63 months, the median PFS was 13.9 months, and the median OS was 54.5 months.

Based on PARP expression, patients were divided into two groups. In 47.68% of the cases (n = 41) we did not find PARP expression or the degree of staining did not reach our limit, while 52.32% (n=45) fell into the PARP positive group. No significant differences were found between the PARP positive and negative groups in the mean age, histological type, degree, stage distribution, or lymph node ratio. The two groups did not differ significantly in terms of the factor most influencing survival, optimal debulking surgery (R0) (51.22% and 48.89%, p = 0.49). The proportion of relapses was higher in the PARP negative group (71.11% and 75.61%), however, the difference was not statistically significant here either. In contrast, there was a significant difference in median progression-free survival. The median PFS was 12.2 months in PARP-positive

patients and 16 months in PARP-negative cases (p = 0.01). The number of deaths did not differ between groups (44.44% and 46.34%, p = 0.86), but similarly to PFS, overall survival rates differed significantly. The median survival was 52 months in the PARP-positive group and 65 months in the PARP-negative group (p = 0.028).

To confirm the above results in our statistical evaluation, we analyzed the effect of PARP positivity on recurrence, relapse within 12 months, risk of death, and OS beyond 32 months by calculating odds ratios (ORs) (at 95% CI). In addition, subgroups were created according to the degree of tumor reduction achieved during primary tumor reduction surgery (R0 or R1) and we attempted to determine a well-defined group where PARP expression contributed most significantly to the change in survival data using ORs. The following results were obtained in the analysis: PARP positivity did not significantly change the chance of recurrence itself (OR 0.79; 95% CI 0.30–2.07, p = 0.638), however, the chance of PFS of less than 12 months was significant (OR 3.73; 95% CI: 1.50–9.26, p = 0.004), so platinum resistance was more common in this group, and the risk of death was minimal in PARP-positive patients, albeit not significantly (OR 0.92; 95% CI: 0.39–2.16, p = 0.859), whereas positivity significantly reduced the patients' chances of OS beyond 32 months (OR 0.318; 95% CI: 0.13– 0.76, p = 0.011). The obtained results were further examined as a function of R0 and R1 resection, thus trying to eliminate the negative biasing effect of macroscopically suboptimal tumor removal on our results. PARP positivity in the R0 group significantly increased the chance of recurrence within 12 months (OR 7.916; 95% CI: 1.47–42.53, p = 0.016) and

consequently reduced the chance of OS beyond 32 months (OR 0.23; 95% CI 0.06-0.83; p = 0.025). The results did not differ significantly in the R1 group.

In our final analysis, we analyzed patient survival data using Kaplan-Meier curves (log-rank test). The median PFS of PARP-negative patients was 16 months (IQR 10.7–35.9 months) compared with 12 months (IQR 6.1–21.8 months) in PARP-positive patients. The difference was significant based on the log-rank test performed (p = 0.01). Total survival data were evaluated and plotted in a similar manner. Median overall survival was 65 months in the PARP negative group (IQR 43.6–110.8 months) and 52 months in the PARP positive group (IQR 36.9–66.7 months). Based on the performed log-rank test, the difference is significant (p = 0.28).

For all examined samples, patients did not receive chemotherapy prior to sampling and received the gold-standard platinum-based treatment after cytoreductive surgery. PARP immunohistochemistry helps to differentiate the group of patients who respond well and poorly to platinum-based therapy. In summary, PARP expression studies provide an estimate of the response to treatment, the expected length of the progression free period, and a platinum-sensitive process in the absence of staining prior to first-line paclitaxel-carboplatin treatment, which can be considered a good prognostic factor for survival.

3.2. The prognostic relevance of PARP expression in ovarian cancer tissue of wild type and BRCA- mutation carrier patients

In our second study, we studied the prognostic value of PARP expression in BRCA wild type and mutation carrier patients. Patients with known BRCA status, follow-up and survival data, and PARP IHC were performed on stored tissue samples were included in our study. The samples were divided into two groups, one consisting of those carrying the BRCA mutation and the other of the BRCA wild type. A total of 104 patients met our inclusion criteria, and in all cases, at the time of tissue sample collection, the patient was chemotherapy naive, so they have not received treatment before. The mean age of our patients was 57.93 ± 11.17 years, in 85.58% of the cases the process was recognized at an advanced stage (FIGO IIIB-IV). Based on the histological examination, a serous process was encountered in most cases (96.15%), and the samples were evaluated in a 2-tier system, high-grade tumors were identified in all cases (100%). In 56 cases (53.85%), macroscopically complete tumor reduction (R0) was achieved during primary surgery. The median follow-up time was 33.58 months, while the median PFS was 13.1 months and the median OS was 72.7 months.

The patient population was divided into two groups based on PARP IHC results. In 32.69% of cases (n = 34) PARP staining could not be identified, while 67.31% (n = 70) showed adequate PARP labeling. We found no significant difference in the pre-treatment characteristics between the PARP negative and positive groups. The factor most influencing survival, the rate of optimal tumor reduction, was similar in the two

groups, 58.82% in the PARP negative group and 51.43% in the PARP positive group (p = 0.48). No significant differences were found between the groups in terms of stage distribution either, the proportion of early stage was 20.59% and 11.43%, while that of advanced stage was 79.41% and 88.57% for PARP negative and positive groups, respectively. There was no significant difference in the number of people carrying the BRCA mutation in the PARP positive and negative groups (28.57% and 32.35%, p = 0.694). There was also no significant difference in the proportion of recurrent cases between the positive and negative groups (85.71% and 76.47%), however, the median PFS was significantly different (11.9 and 20.1 months; p = 0.001). Mortality rates were 40% in the positive group and 35.29% in the negative group (p = 0.646), whereas overall survival was significantly longer in the PARP negative group (49 and 114 months; p = 0.014).

Odds ratios (ORs) (95% CI) were calculated to examine the effect of PARP positivity on recurrence, PFS less than 12 months, mortality, and overall survival less than 32 months. Statistical analysis was also performed adjusted for BRCA status. PARP positivity alone did not result in a significantly higher recurrence or mortality rate, however, the chance of overall survival at less than 32 months was significantly higher (OR 3.3; 95% CI 1.401–7.772; p = 0.006). To clarify the relationship between BRCA status and PARP expression, the comparison was also adjusted for BRCA positive and negative groups. PARP expression in the BRCA wild-type group significantly increased the chance of recurrence (OR 4.059; 95% CI 1.019-16.167; p = 0.047) and resulted in a shorter PFS (OR for recurrence within 12 months: 8.4; 95% CI 2.631- 26.818; p = 0.0003) and shorter

OS values (OR for recurrence within 32 months: 2.765; 95% CI 1,000-7.648; p = 0.05). Elsewhere, the differences were not significant.

In our final comparison, patient survival data were examined using survival curves (Kaplan-Meier curves, log-rank test), based on which we found a significant difference in PFS and OS values between the PARP negative and positive groups. The median PFS was 20.1 months in PARP-negative patients (IQR 12.0–62.7 months) and 11.9 months in PARP-positive patients (IQR 6.4–17.5 months). The difference was significant by log-rank test (p = 0.001). The median OS was 114.6 months (IQR 37.9 to NA) in PARP-negative patients and 49.9 months (IQR: 32.5 to 78.2 months) in PARP-positive patients. The difference was found to be significant by log-rank test (p = 0.014). However, patients' BRCA status alone did not show a significant effect on survival data in either PFS or OS values. The median PFS was 12.6 months (IQR 6.57–21.8 months) in wild-type BRCA patients and 16.4 months (IQR 10.8–30.2 months) in patients with BRCA mutations. The difference was not statistically significant (p = 0.134). The median OS was 70.9 months for BRCA negatives (IQR 29.4–114.6 months) and 89.7 months for BRCA positives (IQR 37.2 - NA months). The performed log-rank test did not confirm a significant difference here either (p = 0.155).

Finally, we examined survival data in the PARP negative and positive groups adjusted for BRCA status. Based on this analysis, PFS was significantly shorter in BRCA wild-type patients, where the tumor tissue showed PARP expression (PFS 10.7 months, IQR 6.3–13.9 months, p = 0.0001), and the shortest also overall survival time (OS 47.2

months). Regarding OS, we obtained the most favorable data in patients with BRCA mutations who were PARP negative, here we could not calculate a median OS value during the follow-up period, as less than 50% of patients died, this value was significantly better for the other subgroups ($p = 0.05$).

Examining the entire patient population, a negative PARP result provided a significant survival advantage for both PFS and OS. Based on the genotype-adjusted subgroup study, it can be concluded that a subgroup with an unfavorable prognosis can be distinguished in BRCA wild-type patients using the PARP study. In the BRCA mutant group, PARP expression was not associated with a less favorable recurrence rate but resulted in poorer OS with marginal significance.

4. DISCUSSION

Treating epithelial ovarian cancer is the biggest challenge of our time for gynecological oncologists. Its mortality far exceeds that of tumors originating from other internal genitals. Its incidence is steadily increasing, mainly in developed Western societies, which can be partly explained by the increase in life expectancy and partly by environmental effects. Its screening is still unresolved despite all attempts, so the proportion of patients with advanced stages is high. In addition to cytoreductive surgery, we have relied on platinum-based chemotherapy treatments for decades. At the same time, these two pillars are the most crucial for patient survival. In our research, we aimed to search for new prognostic factors that can be used to predict the therapeutic response, and optimize the treatment plan of patients.

The genetic background of epithelial ovarian tumor is very heterogeneous and cannot be considered uniform. The high-grade serous (HGSOC) process, which accounts for 70% of all epithelial ovarian cancers, is characterized by a defect in the gene sequence encoding BRCA1 / 2 proteins and other mutations in genes encoding homologous recombination (HR) DNA repair pathway proteins. Mutations in the EMSY, RAD51, ATM, ATR, Fanconi anemia, BARD1, BRIP1, PALB2, RB1, NF1, CDKN2A genes may also lead to HR dysfunction and be identified as risk factors for the development of HGSOC. Mutations in TP 53 are found in almost all cases. LGSOC is a completely different entity from HGSOC. Its characteristic mutations are the differences of the BRAF and KRAS genes, both gene mutations lead to increased activity of the MAPK-mediated

signaling pathway, however, the defects of the TP53 and BRCA genes do not play a significant role in the development of low-grade processes. Deficiencies of the TP53 and BRCA genes in rarer histological subtypes such as clear cell, endometrioid, and mucinous processes also do not play a role in carcinogenesis. Reviewing the molecular genetic background of ovarian cancer, it should be emphasized that the importance of mutations in genes regulating the HR pathway due to its leading role in the development of HGSOC.

In HR deficient cases, mutations in the BRCA gene predominate in inherited or acquired form among epithelial ovarian cancer patients, and the activity of alternative DNA repair pathways have increased importance in these cases for both carcinogenesis and therapeutic response. Among these alternative routes, PARP-mediated DNA repair should be highlighted. The most studied and known member of the poly- (adenosine diphosphate-ribose) polymerase enzyme family is the PARP-1 enzyme, which plays a key role in repairing single-stranded DNA (SSB) breaks. The PARP-1 protein is responsible for 90% of the total nuclear PARP activity. The enzyme is responsible for activating a number of nuclear histones, chromatin proteins, topoisomerases, and DNA protein kinases. Disruption of its function in animal models leads to genome instability and increased sensitivity to cytotoxic agents. Changes in PARP enzyme function, decreased function, can lead to cell death through double-stranded DNA defects caused by the accumulation of SSBs, especially in cells where the HR pathway responsible for repairing DSBs is inadequate. As a result, the study of PARP inhibition has become the focus of

development of anti-tumor therapies in recent years. However, the exact physiological function of the enzyme cannot be deduced so simply. Many of its functions, effects on signaling pathways, and its role in cell reproductive processes and in the regulation of cell death are unclear. In addition to its essential role in maintaining genome stability, it also plays an important role in inducing cell death, as it can not only regulate DNA repair mechanisms but also enhance DNA fragmentation, thus mediating cell death through genome disintegration. The molecular background of this dual effect is not yet clear, however, due to these findings, the exact effect of PARP enzyme inhibition has become one of the most intensively studied areas of anti-tumor research in recent years.

Previous research has focused primarily on the inhibition of the PARP enzyme on HR-deficient cells, however, the malfunction of HR may lead to an increase in the activity of alternative pathways, so the study of PARP activity deserves increased attention. By regulating enzyme activity, the platinum response can be influenced in vitro, as first demonstrated by Wang et al. In their study, MKP-1 was used to regulate PARP enzyme levels in the ovarian tumor cell line, and PARP expression generated by MKP-1 led to platinum resistance in the cells. Elevated PARP levels in tumor cells correlated well with the degree of resistance to cisplatin. Moreover, cells that managed to silence PARP activity repeatedly developed sensitivity to platinum. The results of this study served as an excellent basis for the hypothesis established in our work. Increased PARP expression in the clinic may lead to platinum resistance and thus can be used as a prognostic marker.

In our research, we found that studying PARP protein expression in tissue samples from ovarian cancer patients may help us in achieving this goal. Survival data from our patients categorized by PARP expression differed significantly in both progression-free and overall survival. Survival was significantly better in patients without PARP expression, who accounted for a significant proportion of platinum-sensitive cases. Reviewing the international literature, there are few clinical studies that address the effect of PARP expression on platinum sensitivity. For the majority, the study group of patients was very heterogeneous in terms of both stage distribution and histological subtypes. Based on the number of cases examined, our study does not involve the highest number of patients, however, the high degree of homogeneity of the population we selected offsets this. However, the greatest value of our research is given by the fact that we had the opportunity to further categorize and refine our results by knowing the mutation of BRCA, another gene that regulates the DNA repair pathway. Knowing BRCA status, we were able to identify a group of patients with very unfavorable survival. In addition to the wild status of the BRCA gene, the group was characterized by the presence of PARP expression. From an international perspective, our work is unique in that no such relationship has been previously identified.

Based on our results, examination of PARP expression is a good indicator of decreased sensitivity to DNA damaging effects such as platinum-based chemotherapy. This phenomenon may be stronger if other DNA recovery pathways work properly. This

hypothesis is confirmed by our results that PARP expression means poorer survival in BRCA wild-type patients.

We can state that the evaluation of the function of known DNA repair pathways in everyday clinical work can help us to estimate the therapeutic response of patients, the test method used in our work is easy to reproduce and can be well applied in practice. The special feature of our research is not only the demonstration of the prognostic value of the PARP immunohistochemistry test, but also the fact that we were able to prove its applicability to BRCA status in a homogeneous, well-selected group of patients in a unique way.

5. SUMMARY OF MAJOR RESULTS AND SCIENTIFIC NOVELTIES

- PARP immunohistochemistry helps to differentiate the group of patients who respond well and poorly to platinum-based treatment.
- Based on the examination of PARP expression, the response to treatment, the expected length of the progression-free period and the platinum-sensitive process in the absence of staining can be estimated before the first-line paclitaxel-carboplatin treatment, which can be considered a good prognostic sign for survival.
- Examining the entire patient population, a negative PARP result provided a significant survival advantage for both progression-free survival and overall survival.
- Our research is unique because not only did we study the effect of PARP expression on disease outcome, but we examined the effect of PARP expression among BRCA wild-type and BRCA mutation carrier patients.
- Based on the genotype-adjusted subgroup analyses, it can be concluded that a subgroup with an unfavorable prognosis can be identified in BRCA wild-type patients using the PARP IHC.
- Based on our results, we identified a group of patients with markedly poor prognosis, they are BRCA wild-type patients with strong expression of the PARP enzyme on their tumor tissue.
- Carrying the BRCA mutation did not result a significantly better survival data, but the trend was positive.

6. PUBLICATIONS

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List of publications related to the dissertation

1. **Molnár, S.**, Vida, B., Beke, L., Méhes, G., Póka, R.: The Prognostic Relevance of Poly (ADP-Ribose) Polymerase Expression in Ovarian Cancer Tissue of Wild Type and BRCA-Mutation Carrier Patients.
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