P-ISSN 0215-7284
e-ISSN 25279106
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Correlation between Poly ADP Ribose Polymerase (PARP) expression with Chemotherapy Response in Ovarian Carcinoma

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Received : 08-11-2022
Accepted : 22-11-2022
Published : 31-01-2026

ABSTRACT

Background
Germline mutations in BRCA1 and BRCA2 are high risk factors for ovarian and breast cancer. The risk of ovarian cancer in BRCA1 mutation carriers is 16-68% and 11-30% in BRCA2 mutation carriers.[1,2] The enzyme poly ADP ribose polymerase (PARP) plays an important role in DNA damage repair and genome stability and cancer cells change its regulation as a way for tumor cells to survive cell death due to chemotherapeutic agents.[3,4] Positive PARP expression is associated with high-grade tumors. advanced stage and is an indicator of aggressive disease. The aim of this study was to examine the relationship between PARP expression and the response to chemotherapy in ovarian carcinoma.

Methods
A cross sectional study was conducted using 34 samples of paraffin blocks and slides of ovarian carcinoma from oophorectomy and biopsy of patients registered at the Anatomical Pathology Department Faculty of Medicine Sriwijaya University/Dr. Mohammad Hoesin Hospital Palembang for the period January 2019 to December 2021. Each sample was stained by PARP monoclonal antibody. Qualitative interpretation by assessing semi-quantitatively, namely assessing the area/proportion (P) and intensity (I) of the polished, the score is obtained by multiplying the area by the intensity, the results are grouped into 2, score 0-4 was a weak expression, score 6 was a strong expression. Analysis of the relationship between PARP expression and response to chemotherapy was performed using Chi-square test and Spearmann correlation.

Results
Chi-square test showed that there was a significant relation PARP expression with chemotherapy response, age, CA 125 levels post chemotherapy and stage with p values were 0.008, 0.005, 0.020 dan 0.006 respectively. There was no relation between PARP expression with histopathology subtype with p values was 0.053.

Conclusion
There is a significant correlation between PARP expression with chemotherapy response, age, CA 125 levels post chemotherapy and stage in ovarian carcinoma

Keywords: PARP expression, ovarian carcinoma, chemotherapy response, histopathology subtype

P-ISSN 0215-7284
e-ISSN 25279106
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INTRODUCTION

Ovarian cancer is the second-most common ovarian cancer in western countries and has the worst prognosis and highest mortality rate.[5] Genomic instability is a hallmark of ovarian cancer, with nearly half of ovarian cancers having defects in one or more pathways DNA repair.[6-8] Gene mutations that often occur in ovarian carcinoma are BRCA1 and BRCA2. The risk of ovarian cancer increases by 16–68% in BRCA1 carriers and 11–30% in BRCA2 carriers.[9,10]

Poly ADP ribose polymerase is an enzyme found in nucleus and is activated when DNA is damaged. PARP1 is the subtype that plays the most role in the base excision repair (BER) pathway in single strain break (SSB) DNA repair. PARP1 activation also plays a role in the processes of cell death, transcription regulation, inflammation, and chromatin modification. BRCA1 and BRCA2 are tumor suppressor genes that are important in repairing DNA double-strand breaks (DSB) through the homologous recombination (HR) mechanism.[6,8]

The SSB replication and repair by PARP1 is an important component of cancer cell survival. When PARP is inhibited, unrepaired SSBs will gradually accumulate and degrade into cytotoxic DSBs, but cancer cells treated with BRCA1 and BRCA2 lose the ability to repair DSBs through the HR mechanism, resulting in genome instability and cancer cell death.[6,7]

The current standard of care for ovarian cancer patients is debulking surgery followed by platinum-based chemotherapy, especially a combination of carboplatin and paclitaxel.[11,12] The initial response to this combination therapy is very high (65–80%), but after several treatments, patients experience resistance. cisplatin, which then causes tumor recurrence.[11-14] Poly ADP ribose polymerase inhibitors (PARPi) are one of the newest therapeutic approaches for the treatment of ovarian cancer. These drugs target the DNA damage response in breast cancer and ovarian cancer with BRCA1/2 mutations.[6]

PARP immunohistochemical examination can predict the patient's response to chemotherapy so the choice of therapy can be considered. Westiningrum et al. said that the higher the PARP expression, the higher the resistance to platinum chemotherapy. Based on this, PARP immunohistochemical examination can be a biomolecular marker for predicting response to platinum-based chemotherapy.[3] Godoy et al. stated that epithelial ovarian cancer (EOC) with strong PARP expression is associated with advanced high-grade tumors and has a complete response to first-line chemotherapy. This research also shows that PARP expression is an indicator of aggressive disease. [4] However, in Indonesia itself, PARP status screening has not become the standard standard for ovarian carcinoma patients, especially in Palembang.

METHODS

This research is a descriptive analytical study with a cross-sectional design to determine the relationship between PARP expression and response to chemotherapy in ovarian carcinoma at the Anatomic Pathology Department of Sriwijaya University/Dr. Hospital. Mohammad Hoesin Palembang for the period January 1st, 2019 to December 31st 2021.

In this investigation, 34 archival samples of paraffin/formalin fixed paraffin embedded (FFPE) blocks from all cases of ovarian cancer from oophorectomy or biopsy that had been histopathologically diagnosed were employed. Using a purposive sampling strategy that satisfied the inclusion and exclusion criteria, the research sample was derived retrospectively from a population that was easily available. Following the block's cutting, the tissue was subjected to an immunohistochemical stain using a monoclonal primary antibody against PARP alpha (clone GT6212, Genetex, USA).

The evaluation of PARP expression is categorized as semiquantitative, implying that the area/proportion (P) and intensity (I) of the stained are assessed. A score of 0–3 corresponds to the stained area of cells in the tumor and a score of 0–3 to the degree of PARP expression. The area multiplied by the intensity yields the score, and the outcomes are separated into two distinct groups: 0–4 indicates low expression, whereas ≥6 indicates strong expression. Two researchers performed the interpretation. After that, a DP 21 camera on an Olympus type BX51 binocular light

Maj Patol Indones 2026; 35(1): 1025-1034
DOI: 10.55816/mpi.v35i1.661

P-ISSN 0215-7284
e-ISSN 25279106
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microscope was utilized for taking documentation photos of the stained tissue. A well-differentiated hepatocellular carcinoma individuals acted as the study's positive control. In this research, diaminobenzidine tetrahydrochloride (DAB) was the chromogen.

The proportion of research subjects based on clinicopathological variables, including age, histopathological subtype, post-chemotherapy Ca 125 levels, and stage, as well as based on the independent variable, PARP expression, and the dependent variable, chemotherapy response, had been determined through univariate (descriptive) analysis. The goal of bivariate analysis is to figure out whether PARP expression in ovarian cancer corresponds with clinicopathological features and chemo-therapeutic response. Using the Chi-Square test or Spearmann correlation, this research was performed to see whether there was a relationship between PARP expression and clinicopathological variables, such as age, histological subtype, post-chemotherapy Ca 125 levels, and stage. If the p-value with a 95% confidence interval was less than 0.05, it considered to be significant. A statistical program named the Statistical Program for Social Science (SPSS) version 26.0 tools were utilized for data analysis. The Doctor Mohammad Hoesin General Hospital in Palembang has granted ethical approval for this research, with ethical number 144/kepkrsmh/2022, which complies with seven 2011 WHO guidelines.

OUTCOMES

Distribution of Ovarian Cancer's Clinicopathological Features, PARP Expression, and Chemotherapy Response of Ovarian Carcinoma.

The age, PARP expression, chemo-therapy response, and post-chemotherapy distribution of clinicopathological features Table 1 displays the ovarian cancer stage and Ca 125 levels. Table 1 shows the age group under 50 is the largest, with 18 samples (52.9%), followed by the age group over 50 with 16 samples (47.1%). High grade serous carcinoma was the most common histological category, 10 samples (29.4%) and. Mucinous carcinoma was next with 7 samples (20.6%), low grade serous carcinoma with 6 samples (17.6%), endometrioid carcinoma with 6 samples (17.6%), and clear cell carcinoma with 5 samples (14.7%). Nineteen samples (55.9%) showed strong PARP expression, whereas fifteen samples (44.1%) showed weak PARP expression. Thirteen patients (38.2%) were unresponsive to chemotherapy, whereas twenty-one (61.8%) exhibited a response. The majority of the study's samples had Ca 125 post chemotherapy levels of less than 35 U/ml, namely in 24 samples (70.6%) and 10 samples (29.4%), with levels beyond 35 U/ml. 22 samples, or 64.7% of the patients in this study were in stage III.

Table 1. Lists the features of the sample according to clinicopathology, PARP expression, Ca 125 levels before surgical procedures, Ca 125 levels after chemotherapy, and chemotherapy response.

Variabel	N	%
Age		
<50	18	52.9
≥50	16	47.1
Histological subtype		
Low grade serous carcinoma	6	17.6
High grade serous carcinoma	10	29.4
Mucinous carcinoma	7	20.6
Endometrioid carcinoma	6	17.6
Clear cell carcinoma	5	14.7
PARP expression		
Strong	19	55.9
Weak	15	44.1
Chemotherapy response		
Responsive	21	61.8
Unresponsive	13	38.2
Ca 125 levels after chemotherapy		
>35	24	70.6
<35	10	29.4
Stage		
I	5	14.7
II	3	8.8
III	22	64.7
IV	4	11.8

Maj Patol Indones 2026; 35(1): 1025-1034
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P-ISSN 0215-7284
e-ISSN 25279106
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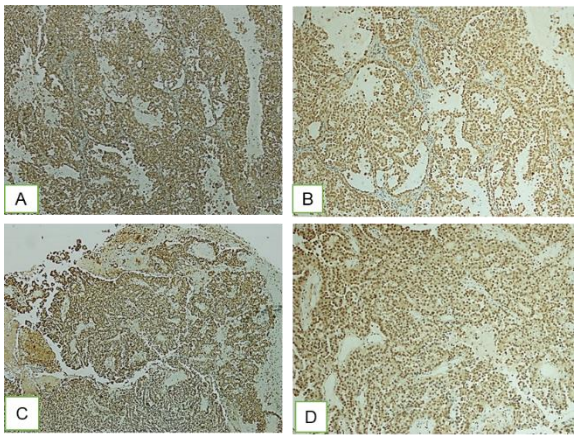

Figure 1. A. Image of strong PARP expression in case number 9 (40 times). B. Image of strong PARP expression in case number 9 (100 times). C. Image of strong PARP expression in case number 14 (40 times). D. Image of strong PARP expression in case number 14 (100 times).

Semiquantitative PARP expression involves measuring the stained area (P) and intensity (I). The area multiplied by the intensity yields the score. Two categories are generated based on the results: 0–4 shows weak expression, whereas ≥6 shows strong expression. The area of tumor cells stained was scored as 0 if stained ≤20%, 1 stained 20–50%, 2 stained 51–80%, and 3 if stained >80%. PARP expression intensity: 0 if not stained, 1 if stained weak brown or light brown, 2 if stained medium brown or light brown, and 3 if stained strong brown.[3]

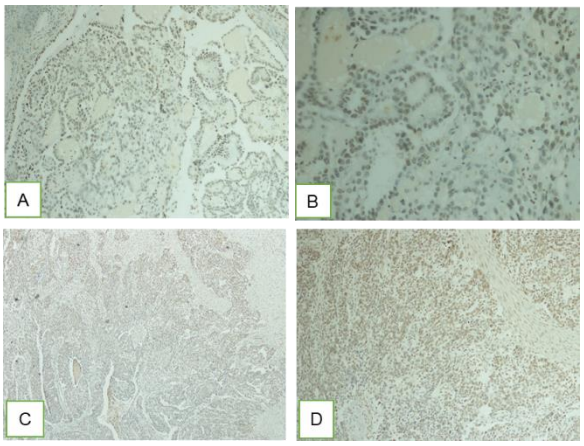

Figure 2. A. Image of weak PARP expression in case no. 18 (40 times magnification) B. Image of weak PARP expression in case no. 18 (100 times) C. Image of weak PARP expression in case no. 22 (40 times magnification) D. Image PARP expression was weak in case no. 22 (100 times magnification).

Two-Phase Analysis

1. Association between ovarian cancer clinicopathological features and PARP expression.

1.1 Age and PARP expression relationship.

The chi square test (Table 2) was used to evaluate the correlation between PARP expression and age. The results showed that there was a relationship between the two variables (p=0.005). In 12 samples (35.3%), the age group with weak PARP expression was most frequently found to be under 50 years old, whereas in 3 samples (8.8%), it was found to be above 50. Conversely, in 13 samples (38.2%) and 6 samples (17.6%), the age group <50 years old was the one in which significant PARP expression was more frequently observed.

Table 2. Relationship between PARP expression and age.

Age	PARP expression				Total		*p
	Weak		Strong				
	N	%	N	%	N	%	
<50 yars old	12	35.3	6	17.6	18	52.9	0.005
≥50 years old	3	8.8	13	38.2	16	47.1	

*Chi square test, significant if p<0.05.

Maj Patol Indones 2026; 35(1): 1025-1034
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P-ISSN 0215-7284
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1.2. Association between PARP expression and histopathological subtypes

There was no correlation (p=0.053) between PARP expression and histological subtypes, according to an analysis of the link between the two (Table 3). Six samples (17.6%) of the histopathological subtype group with strong PARP expression were discovered in HGSC, whereas five samples (14.7%) of the histopathological subtype group with weak PARP expression were detected in LGSC.

Table 3. Correlation between PARP expression and histopathological subtypes.

Histopathological subtypes	PARP expression				Total		*p
	Strong		Weak				
	N	%	N	%	N	%	
LGSC	1	2.9	5	14.7	6	17.6	
HGSC	6	17.6	4	11.8	10	29.4	
MC	4	11.8	3	8.8	7	20.6	0.053
EC	4	11.8	2	5.9	6	17.6	
CCC	4	11.8	1	2.9	5	14.7	

**Spearmann Correlation Test*, significant if *p* <0.05.

1.3. Relationship between PARP expression and Ca 125 levels after chemotherapy

Analysis of the relationship between PARP expression and post-chemotherapy Ca 125 levels was carried out using the Fisher exact test (Table 4), which showed that there was a relationship between PARP expression and post-chemotherapy Ca 125 levels (p=0.002). The weak PARP expression sample group was often found in samples with Ca 125 levels <35 U/ml, namely in 14 samples (41.2%), while the strong PARP expression sample group was often found in samples with Ca 125 levels >35 U/ml, namely in 9 samples (26.5%).

Table 4. Relationship between PARP expression and Ca 125 levels after chemotherapy.

Ca125 post-chemotheraphy concentration	PARP expression				Total		*p
	Strong		Weak				
	N	%	N	%	N	%	
<35 U/ml	10	29.4	14	41.2	24	70.6	0.002
>35 U/ml	9	26.5	1	2.9	10	29.4	

*Fisher exact test, significant if p <0.05.

1.4. Relationship between PARP expression and stage.

Analysis of the relationship between PARP expression and stage was carried out using the Spearmann correlation test (Table 5) which showed that there was a relationship between PARP expression and stage (p=0.006). The higher the stage of ovarian carcinoma, the stronger the PARP expression.

Table 5. Relationship between PARP expression and stage.

Stage	PARP expression				Total		*p
	Strong		weak				
	N	%	N	%	N	%	
I	0	0.0	5	14.7	5	14.7	
II	2	5.9	1	2.9	3	8.8	
III	13	38.2	9	26.5	13	64.7	0.006
IV	4	11.8	0	0	4	11.8	

*Spearmann correlation test, significant if p <0.05.

Maj Patol Indones 2026; 35(1): 1025-1034
DOI: 10.55816/mpi.v35i1.661

P-ISSN 0215-7284
e-ISSN 25279106
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2. Relationship between PARP expression and chemotherapy response.

Analysis using the chi-square test in Table 2 shows that there is a relationship between PARP expression and chemotherapy response, and the results obtained were significantly significant with a p-value of 0.008. PARP expression was stronger in samples that did not respond to chemotherapy (32.4%).

Table 6. Relationship between PARP expression and chemotherapy response.

PARP expression	Chemotherapy response				Total		*p
	Responsive		Unresponsive				
	N	%	N	%	N	%	
Strong	8	23.5	11	32.4	18	55.9	0.008
Weak	13	38.2	2	5.9	16	44.1	

*Chi square test, significant if p<0.05.

DISCUSSION

Research based on Zheng et al states that the risk of ovarian cancer increases with increasing age and reaches a peak at the ages of 50 years old and 80 years old.[13] This is because old age is associated with decreased exposure to estrogen during menopause. Several studies have also shown that the incidence of ovarian carcinoma increases in women over 50 years old.[13-15] Therefore, in this study, age 50 years old was used as a cut-off.

Ovarian carcinoma often occurs at the age of 63 years old and over and rarely occurs at the age of 40 years old and under.[16] A shift in the incidence rate of ovarian carcinoma in women of younger age (<50 years old) is starting to occur, as this study shows that ovarian carcinoma is more common in those under age 50 years old, namely in 18 samples (52.9%). The age shift in the incidence of ovarian carcinoma is in line with previous research conducted by Lheureux et al.[17] Ovarian carcinoma at age less than 50 years old is associated with the presence of genetic mutations. In particular, mutations in BRCA1 and BRCA2 are major genetic risk factors. Women who carry germline mutations in BRCA1 and BRCA2 have a substantially increased risk of ovarian, tubal, and peritoneal cancer of approximately 20%-50% in BRCA1 and 10%-20% in BRCA2 with an average patient age of the mid-40s.[14]

Risk factors that play a role in increasing the risk of ovarian carcinoma include age, reproductive factors such as early menarche and late menopause, a low parity rate, hormonal factors, smoking, and obesity. The most frequent histopathological subtype is HGSC, which is in line with this study.[18,19] Similar results were also found in Rikka et al.'s research at Dr. Moh Hoesin Hospital Palembang for the period 2013–2016. 20 High levels of HGSC are associated with type II ovarian tumors, which tend to grow more aggressive, quickly metastasize, and have genetic mutations in TP53 and BRCA1/2. [15,17] Type II tumor cell precursors can originate from the fallopian tubes, where the combination of TP53 mutations and environmental stressors causes epithelial cells in the fallopian tubes to undergo neoplastic changes.[21]

One of the most fatal gynecological cancers, ovarian carcinoma is frequently detected in stages III and IV. This study is consistent with Brahmantara et al.'s research, which found that ovarian cancer was already at stage III when it was detected. [22] Because ovarian carcinoma does not often present with specific signs in its early stages, Rustin et al.'s investigation also discovered that when the cancer had already progressed to stages III and IV.[23]

Relationship between PARP expression and age

Strong PARP expression was more common in the >50-year-old group, with 13 samples (38.2%) compared to 6 samples (17.6%) in the <50 years old group. This is in line with the research of Grant et al.[18] Aging is a progressive decline in biochemical and physiological functions that depends on time. Oxidative DNA damage is a major factor associated with age-related diseases that disrupts various genes

Maj Patol Indones 2026; 35(1): 1025-1034
DOI: 10.55816/mpi.v35i1.661

P-ISSN 0215-7284
e-ISSN 25279106
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associated with DNA repair and cell proliferation, including PARP. Oxidative DNA damage activates the NAD-dependent DNA repair enzyme, PARP, which is involved in BER repair. Grant et al have shown that PARP activity is higher in various aged tissues (24 months) than in young tissues (3 months). [18]

Association between PARP expression and histopathological subtypes

The results of this study showed that PARP was strongly expressed in the majority of the research samples, namely 19 (55.9%) samples. In this study, 6 of 10 HGSC samples showed strong expression of PARP; CCC showed strong expression of PARP in 4 of 5 samples; EC showed strong expression in 3 of 6 samples; MC showed strong expression in 4 of 7 samples; and LGSC showed strong expression in 1 of 6 samples. PARP was expressed in all histopathological types in the study samples, and based on statistical assessment, histopathological type did not influence PARP expression (p=0.26).

Witjes et al.'s meta-analysis study stated that the risk of BRCA germline mutations in all OCs was 16.8%. The risk of BRCA mutation in HGSC is 22%, in EC is 5.8%, in CCC is 3%, and in MC is 2.5%, where ovarian cancer with BRCA mutations relies on alternative DNA repair mechanisms that depend on PARP. 25 This is in line with the results of this study, where those that showed stronger expression results were HGSC. However, in CCC, EC, and MC, this is not consistent because the CCC, MC, and EC in this study were at advanced stages III and IV, where advanced stages already showed metastasis and aggressive tumor behavior.[4]

Relationship between PARP expression and Ca125 levels after chemotherapy

An important marker for monitoring the response to ovarian cancer treatment is Ca 125. Increases and decreases in serum Ca 125 levels correlate with progression or regression in 90% of ovarian carcinoma patients. Assessment of cancer progression according to the Gynecologic Cancer Intergroup (GCIG) is by observing changes in Ca 125 levels at least in two examinations, with a gap between the first and second examinations of 1 week. In patients who do not reach normal limits after chemotherapy, progression is defined as two tests with results that are at least double the lowest Ca 125 level the patient has ever achieved. [26]

In this study, the sample group with strong PARP expression was found in samples with Ca125 levels >35 U/ml, namely in 9 samples (26.5%), while the sample group with weak PARP expression was mostly found in samples with Ca125 levels <35 U/ml, namely in 14 samples (41.2%). Statistical results showed that there was a relationship between PARP expression and Ca 125 levels after chemotherapy (p=0.010). Ninuk et al's research shows that a prolonged decrease in CA 125 levels reflects a poor response to therapy. In some patients, CA 125 levels >70 units/mL checked at baseline before administering the third chemotherapy is usually a strong predictor of recurrence or death. The half-life of CA 125 measured before chemotherapy is started is also an independent prognostic factor for survival, progression, and the chance of complete remission. [27]

Relationship between PARP expression and stage

Analysis of the relationship between PARP expression and stage showed that there was a relationship between PARP expression and stage (p=0.021). The higher the stage of ovarian carcinoma, the stronger the PARP expression. Godoy et al research showed that overexpression of PARP is associated with advanced stages and indicates more aggressive tumor behavior. [4]

Hyperactive poly ADP ribose polymerase 1 upregulates inflammatory signaling factors such as NF-κB, which then leads to further inflammation and tumorigenesis. The inflammatory signal NF-kB is a transcription factor that can activate proinflammatory transcription. The interaction between NF-kB and PARP1 increases the levels of proinflammatory cytokines such as tumor necrosis factor (TNFα) and interleukin 6 (IL6), which will also initiate tumor-promoting inflammation. On the other hand, chronic NF-κB-mediated inflammation facilitates tumors to develop multiple malignant

Maj Patol Indones 2026; 35(1): 1025-1034
DOI: 10.55816/mpi.v35i1.661

P-ISSN 0215-7284
e-ISSN 25279106
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phenotypes that can escape immune surveillance. An important role NF-kB also plays in carcinoma development, metastasis, and angiogenesis.[28]

According to Damayanti et al.'s research, the three-year survival rate for each stage of ovarian carcinoma was 89.3%, 44.4%, and 35.1% for stage I, stage II, and stage III patients, and no patients survived. up to 3 years at stage IV. [29] Research on the relationship between PARP expression and the FIGO stage of ovarian carcinoma is very limited. Katarina et al.'s research on cervical carcinoma showed that high PARP-1 expression had a 10.5 times greater prevalence risk of becoming stage III-IV than low PARP-1 expression. This explains that hyperactivation of PARP-1 plays a role in the process of tumorigenesis and progression. [30]

Relationship between PARP expression and chemotherapy response.

Strong expression of PARP is a reflection of high levels of DNA damage. Westiningrum et al.'s research states that the higher the PARP expression, the higher the resistance to platinum chemotherapy.[3] Godoy et al.'s research shows that PARP expression is an indicator of aggressive disease.[4] This is in line with the results of this study. Strong PARP expression was found in many samples that did not respond to chemotherapy, namely in 11 samples (32.4%). The results of this study were proven to be statistically significant with a p-value of 0.008.

One of the mechanisms by which cisplatin works as a chemotherapy agent is by activating JNK 1/2 and p73, encouraging the formation of the JNK 1/2-P73 complex, thereby causing apoptosis and inducing DNA damage. JNK1/2 activity can be suppressed by increasing MKP-1 expression. Decreased JNK1/2 activity by MKP-1 overexpression may decrease cisplatin sensitivity in cancer cells. JNK phosphorylates serine 257 and serine 782 and then phosphorylates PARP-1, promoting PARP-1 ubiquitination to regulate PARP-1 degradation. Suppression of JNK1/2 causes reduced PARP1 phosphorylation, decreased PARP degradation, and high PARP levels. [31]

The enzyme poly ADP ribose polymerase (PARP) plays an important role in DNA damage repair and genome stability. BRCA mutations are one of the most common hereditary genetic defects that occur in ovarian cancer patients. Loss of BRCA function leads to genome instability, an increased risk of tumorigenesis, and dysfunctional homologous recombination pathways. In homologous recombination deficiency, mutations in BRCA will disrupt PARP function, causing an accumulation of double-strand DNA damage. Cytotoxic drugs that are supposed to repair DNA damage become less effective due to the high accumulation of DNA damage. [3,4]

CONCLUSION

There was a significant relationship between PARP expression and response to chemotherapy, age, and post-chemotherapy Ca 125 levels and stage in ovarian carcinoma, but there was no relationship between PARP expression and histopathological subtype.

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P-ISSN 0215-7284
e-ISSN 25279106
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DOI: 10.55816/mpi.v35i1.661