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RESEARCH ARTICLE

Poly ADP Ribose Polymerase-1, Lymphovascular Invasion, and Tumor Size as Risk Factors for Regional Metastasis in TNBC

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ABSTRACT

Breast cancer is the leading cause of cancer death in women worldwide, with 458,400 women dying each year. Triple negative breast cancer (TNBC) is a highly invasive subtype of breast cancer that has a high frequency of DNA repair gene mutations that cause overexpression of Poly-(ADP ribose) polymerase (PARP1) which plays a role in DNA repair for cancer cell survival during chemotherapy. This study aimed to determine the role of PARP1 overexpression along with lymphovascular invasion, tumor size, and degree of differentiation as risk factors for regional metastasis in triple negative breast cancer. This is a retrospective case-control study that observed the association between PARP1 overexpression with lymphovascular invasion, tumor size, and differentiation grade and the incidence of regional metastasis. Data were analyzed using SPSS 21.0 to find the Odds ratio (OR), 95% CI, and significance (p) of each risk factor. The results of this study show that 40 study samples, 23 samples (57.5%) showed strong PARP1 expression. Multivariate analysis showed that strong expression of PARP1 overexpression (p: 0.030; OR: 5.926; 95% CI: 1.267-27.71), primary tumor size (p: 0.031; OR: 14.327; 95%CI: 1.27-161.07), and LVI (p: 0.045; OR: 6.016; 95%CI: 1.04-34.72), were significantly associated with regional tumor metastasis, while tumor differentiation grade was not. Strong PARP1 expression, LVI, and tumor size are risk factors for regional metastasis in TNBC and can be used to determine patient prognosis.

INTRODUCTION

Breast cancer is the leading cause of cancer death in women worldwide. Triple negative breast cancer (TNBC) is a highly invasive subtype of breast cancer that has a high frequency of DNA repair gene mutations that cause overexpression of Poly-(ADP ribose) polymerase (PARP1) which plays a role in DNA repair for cancer cell survival during chemotherapy. TNBC is aggressive with a high risk of Metastasis, high Recurrence in the first and third years after diagnosis, and lower life expectancy compared to other subtypes (Torre, et al., 2015; Birkbak, et al., 2012).

The text discusses breast cancer (Breast Cancer, KPD), specifically triple-negative breast cancer (TNBC), which has high molecular heterogeneity and varying chemotherapy responses. Breast cancer remains a leading cause of cancer mortality among women globally, with a notable incidence increase in Southeast Asia. The TNBC subtype accounts for 10-20% of breast cancer cases and is characterized by the absence of hormone and HER2 receptors, making it less responsive to conventional therapies but more sensitive to chemotherapy (Birkbak, et al., 2012; Anders, et al., 2010).

Genetic mutations, particularly in BRCA1/2, influence chemotherapy response in TNBC. BRCA mutations hinder DNA repair, making cancer cells more susceptible to DNA-damaging agents like

chemotherapy. The role of Poly (ADP-ribose) polymerase 1 (PARP1) is highlighted, as PARP1 helps repair DNA and supports angiogenesis in TNBC, particularly when BRCA-related repair is compromised. PARP inhibitors have shown promise in TNBC patients with BRCA mutations (Aleskandarany, et al., 20115; Gonzalez-Angulo, et al., 2011).

Another focus is the PI3K/AKT signaling pathway, which affects cell survival, proliferation, and angiogenesis in TNBC. Mutations in PIK3CA and PTEN, components of this pathway, are common and contribute to therapy resistance. Personalized medicine approaches, which include evaluating the role of PARP1 and Protein Kinase β/AKT expressions, are recommended to improve chemotherapy responses for TNBC patients (Anders, et al., 2010; Annunziata and Bates, 2010). This research aims to support personalized treatment strategies for TNBC by identifying genetic and molecular markers for better-targeted therapies.

METHOD

This study is a retrospective case-control study, an observational study design that is often used to investigate the relationship between a particular exposure and an outcome (usually a disease or health condition) by looking back (retrospectively) at previous risk factors or characteristics. This study was conducted on TNBC patients at Sanglah Hospital, Bali with a sample size of 40 TNBC patients at Sanglah Hospital, Bali from 2016-2017. The bivariate analysis test used the Chi Square method and the multivariate analysis test used binary logistic regression with a significance level of $p < 0.05$.

RESULTS

Table 1.Clinicopathological Characteristics of Research Samples

Variables	**Control**	**Case**	**P**
	N (-)	**There is no (+)**	
Age	46.60±10.709	41.20±9.356	0.108
Degree of Differentiation			
Low Class	9 (45.0%)	4 (20.0%)	0.091
High grade	11 (55.0%)	16 (80.0%)	
Tumor Size			
T1-2	10 (50.0%)	1 (5.0%)	0.001*
T3-4	10 (50.0%)	19 (95.0%)	
LVI			
Negative	14 (70.0%)	4 (20.0%)	0.001*
Positive Things	6 (30.0%)	16 (80.0%)	
PARP-1 **Low Expression** **Strong Expression**	 12 (60.0%) 8 (40.0%)	 5 (25.0%) 15 (75.0%)	0.025*

Table 2. Bivariate Analysis

		CASE	**CONTROL**	**P**	**OR**	**IK 95%**
		No(+)	N(-)			
	Tall	16 (80.0%)	11 (55.0%)	0.091	-	-

Degree Of Differentiation	Low	4 (20.0%)	9 (45.0%)	(Chi-Square)		
Tumor size	T3-4	19 (95.0%)	10 (50.0%)	0.001* (Chi-Square)	19,000	**2.119-170.383**
	T1-2	1 (5.0%)	10 (50.0%)			
LVI	Positive	16 (80.0%)	6 (30.0%)	0.001* (Chi-Square)	9,333 people	**2.180-39.962**
	Negative	4 (20.0%)	14 (70.0%)			
PARP1	Strong	15 (75.0%)	8 (40.0%)	0.025* (Chi-Square)	4,500 people	**1,166-17,373**
	Weak	5 (25.0%)	12 (60.0%)			
Total		**20(100%)**	**20(100%)**			

***PARP1*:**

Table 1 and table 2 show that High PARP 1 expression was a significant risk factor for regional metastasis, with an adjusted p value of 0.030. The analysis showed that the odds ratio (OR) for this association was 5.926, with a 95% confidence interval of 1.267 to 27.71, indicating an increased risk of regional metastasis in patients with high PARP 1 expression.

LVI:

Positive lymphovascular invasion (LVI) was a significant risk factor for regional metastasis, with an adjusted p value of 0.045. The analysis showed that the odds ratio (OR) for this association was 6.016, with a 95% confidence interval of 1.04 to 34.72, indicating an increased risk of regional metastasis in patients with positive LVI.

Tumor Size:

Primary tumor size T3-T4 was a significant risk factor for regional metastasis, with an adjusted p value of 0.031. The analysis showed that the odds ratio (OR) for this association was 14.327, with a 95% confidence interval of 1.27 to 161.07, indicating an increased risk of regional metastasis in patients with primary tumor size T3-T4.

Degree of Differentiation:

The degree of cell differentiation was not a significant risk factor for regional metastasis, with an adjusted p-value of 0.314.

DISCUSSION

PARP1 (Poly (ADP-ribose) polymerase 1) is an enzyme that plays an important role in DNA repair, especially in repairing DNA damage due to oxidative stress and various external factors. In the context of cancer, PARP1 has been widely studied in relation to its role in tumor development and spread, including metastasis. Metastasis is the process of spreading cancer cells from their original location to other locations in the body, such as lymph nodes (regional metastasis) or other organs (distant metastasis). PARP1 can affect metastasis through several mechanisms, including:

1. DNA Repair and Tumor Cell Survival: PARP1 helps tumor cells repair their DNA damage, allowing these cells to survive despite stress or genetic damage that would kill normal cells. Thus, PARP1 helps maintain the proliferative ability of cancer cells and supports the invasive properties necessary for metastasis (Anders, et al., 2010).
2. Response to Hypoxia: The tumor environment is often hypoxic (lack of oxygen), which can increase PARP1 expression. Hypoxia and PARP1 together drive cancer cells to increase their ability to migrate and penetrate surrounding tissues (Mazzotta, et al., 2016).
3. Metastasis Gene Regulation: PARP1 is involved in regulating the expression of various genes related to the movement and invasion of cancer cells. High PARP1 activity can increase the expression of matrix metalloproteinase (MMP) proteins and transcription factors such as NF-κB, which play a role in damaging the extracellular matrix, thereby facilitating the movement of cancer cells to other areas (Rojo, et al., 2012).

Several studies have shown that high PARP1 expression is associated with an increased risk of regional metastasis, especially in the lymph nodes. These findings suggest that PARP1, which plays a role in DNA repair, also facilitates cancer aggressiveness and local migration ability to the lymph nodes. Therefore, high PARP1 expression levels are often considered a risk factor for regional metastasis in several types of cancer, such as breast, prostate, and ovarian cancer (Toss, et al., 2015; Abramson, et al., 2015).

Understanding the role of PARP1 in metastasis provides an opportunity for the development of more targeted cancer therapies, particularly using PARP inhibitors (PARPi). PARP inhibitors work by inhibiting PARP1 function, thereby interfering with the ability of cancer cells to repair their DNA, which in turn may reduce the chances of cancer cells surviving and spreading. Several PARP inhibitors, such as olaparib and niraparib, have been approved for use in patients with several types of cancer, particularly those with BRCA deficiency or other genetic vulnerabilities (Mazzotta, et al., 2016).

PARP1 as a Risk Factor for Regional Metastasis: We suspect that metastasis occurs due to the failure of anticancer therapy to cause cancer cell death due to the DNA damage response that overcomes the DNA damage. The main DDR mechanism in the occurrence of single strand breaks (SSB) is Poly-ADP ribose polymerase (PARP) through base excision repair (BER) and in double strand breaks (DSB) is BRCA through homologous recombination. With increased PARP activity (especially in TNBC with BRCA mutations) the DNA repair mechanism will result in genomic instability in the tumor resulting in aggressive and large tumors (Mazzotta, et al., 2016; Peralta-Leal, et al., 2008; Aleskandarany, et al., 2015).

LVI (Lymphovascular Invasion) and the size of the primary tumor are important factors in determining the risk of regional metastasis, which is the spread of cancer cells to nearby lymph nodes or surrounding tissues. Here is an explanation of both:

1. **LVI (Lymphovascular Invasion)**: LVI is the presence of cancer cells in the blood vessels or lymphatics surrounding the primary tumor. LVI indicates that the cancer has the ability to spread through the bloodstream or lymphatic system, which may increase the risk of regional metastasis. The presence of LVI is often considered a sign of tumor aggressiveness, and patients with LVI are generally at higher risk of developing lymph node metastases (Bianchini, et al., 2016; Calvert and Azzariti, 2011).
2. **Primary Tumor Size:** The size of the primary tumor is also an important predictor of the likelihood of regional spread. The larger the tumor, the greater the risk of lymph node metastasis. In some cancers, such as breast cancer and thyroid cancer, a larger tumor size (eg, greater than 2 cm or 5 cm, depending on the type of cancer) may indicate a higher potential risk for metastasis (Kumar and Aggarwal, 2016; Le Du, et al., 2015).

The combination of LVI and large tumor size often indicates a higher risk of metastasis than other factors. Clinical assessment with further examinations such as biopsy, ultrasound, CT scan, or PET scan are usually performed to evaluate whether there has been metastasis to lymph nodes or other tissues (Lehmann, et al., 2011; Lehmann, and Pietenpol, 2014; Perou, et al., 2000).

LVI and Primary Tumor Size for Regional Metastasis: Lymphovascular Invasion: The initial step of cell metastasis via the lymphovascular pathway. Larger tumor sizes result in increased cell numbers and thus increased risk of cell spread (Bianchini, et al., 2016; Le Du, et al., 2015).

CONCLUSION

PARP1 plays an important role as a risk factor in regional metastasis, primarily through its ability to support cancer cell survival and facilitate tumor cell invasion and migration. High PARP1 expression in cancer is often associated with a poorer prognosis, including the risk of local spread to lymph nodes, making it a potential target for cancer therapeutic intervention.Strong PARP1 expression, LVI, and tumor size are risk factors for regional metastasis in TNBC and can be used to determine patient prognosis.

Ethical approval

The research team strictly followed ethical standards in research,Ethics approval document is available at No. 195/UN4.6.4.5.31/PP36/2017 Udayana University Research Ethics Committee; we ask for consent before becoming a participant, all individual information is kept confidential and is not reported in the paper.

Conflict of Interest

All authors declare no conflict of interest.

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