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Assessment of SF3B1 Expression as a Prognostic Marker for Neoadjuvant Chemotherapy Response in Stage III Triple-Negative Breast Cancer

Desak Made Wihandani*[1], Putu Anda Tusta Adiputra[2], Gede Wikania Wira Wiguna[3], Putu Gede Septiawan Saputra[3], Made Violin Weda Yani[3], Ida Ayu Widya Anjani[3], Wayan Ardyan Sudartha Putra[3], Gede Putu Supadmanaba[1]

Abstract

Background: SF3B1 is a splicing factor that plays a crucial role in cancer progression and is commonly found in various types of solid cancers. However, the reports regarding the clinical implications of SF3B1 in terms of therapy response, survival, and its relationship with patients' clinicopathological features are still limited. This study aimed to assess SF3B1 expression for neoadjuvant chemotherapy response in stage III triple-negative breast cancer.

Methods: This case-control study was conducted at Prof. Dr. I.G.N.G. Ngoerah General Hospital from March to October 2021. Stage III TNBC breast cancer patients who received neoadjuvant chemotherapy were included. Variables assessed included SF3B1 expression, NAC response, and various histological and clinical parameters. Immunohistochemistry (IHC) for SF3B1 expression was performed using the avidin-biotin method. Data analysis involved univariate, bivariate (chi-square), and multivariate (logistic regression) methods using SPSS, with significance set at $p \leq 0.05$.

Results: Analysis showed that high Ki-67, tumor-infiltrating lymphocytes (TILs), and SF3B1 status significantly increased the risk of chemoresistance in TNBC breast cancer (OR=6.4, 95%CI=1.20-34.19, p-value=0.017; OR=4.8, 95%CI=1.05-21.75, p-value=0.031; OR=13.5, 95%CI=1.56-116.24, p-value=0.008, respectively) No significant relationships were found with age, grading, or menopausal status. Multivariate analysis confirmed these variables independently influenced chemoresistance, with aOR=14.4, 95%CI=1.80-115.73 for Ki-67 (p-value=0.012), aOR=6.7, 95%CI=1.12-40.46 for TIL (p-value=0.037), and aOR=13.714, 95%CI=1.56-116.24 for SF3B1 (p-value=0.018).

Conclusion: High SF3B1 expression, alongside high Ki-67 and TIL levels, is potentially a prognostic marker for chemoresistance in stage III TNBC. These findings suggest that targeting SF3B1 could offer a novel therapeutic approach in TNBC patients.

Keywords: Neoadjuvant chemotherapy, Marker, Prognosis, SF3B1, TNBC.

Introduction

Breast cancer is the most prevalent cancer among women worldwide, occurring in both developed and developing countries (1). Currently, the global incidence of breast cancer

1: Biochemistry Department, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia.
2: Surgical Oncology Subdivision, Department of Surgery, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali, Indonesia.
3: Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia.
***Corresponding author: Desak Made Wihandani; Tel: +62 361 222510; E-mail: dmwihandani@unud.ac.id.**
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is approximately 645,000 cases among premenopausal women and 1.4 million cases among post-menopausal women. In Indonesia, breast cancer is also the most common cancer among women, with an incidence rate of 42.1 per 100,000 people and a mortality rate of 17 per 100,000 people (2). Triple-negative breast cancer (TNBC) is a subtype of breast cancer that does not express the three common receptors and is one of the clinically most aggressive subtypes, resulting in a worse prognosis (3). TNBC is classified as a luminal androgen receptor (LAR) subtype, immunomodulatory (IM), mesenchymal (M), mesenchymal-like (MSL), Basal-like 1 (BL-1), and Basal-like 2 (BL-2) because to its substantial genomic and phenotypic diversity and genomic instability (4). This variability also affects the chemotherapy response and recurrence rates of TNBC, which remain difficult to predict. Despite the emergence of several prognostic factors such as p16 and antioxidant capacity ratio (5,6), TNBC still has the poorest prognosis among breast cancer subtypes and difficult to predict, as evidenced by a 5-year survival rate of only 62.1%, compared to 80.8% for non-TNBC subtypes. A crucial determinant of survival rates is the chemotherapy response. Although TNBC is generally chemosensitive, an estimated 20% of TNBC patients exhibit chemoresistance, which cannot be predicted using conventional scoring systems (7).

Alternative splicing (AS) is a process of intron removal from primary transcripts facilitated by the spliceosome. Cancer is known to have different AS patterns compared to normal cells, and splicing aberrations are considered a new hallmark of cancer (8). Mutations, overexpression, or downregulation of spliceosome components such as SRSF1, SRSF6, RBFOX2, SF3B1, SF3B3, and PTBP1, among others, cause these aberrations. Among these splicing factors, SF3B1 is the most extensively studied and characterized. SF3B1 plays a crucial role in the splicing process at the branch point region of introns. It is known to be significant in the progression of both solid and non-solid cancers, such as chronic myelogenous leukemia (CML), pancreatic cancer, colorectal cancer, and breast cancer. SF3B1 mutations are highly prevalent in non-solid cancers and play a significant role. However, in solid cancers, SF3B1 overexpression is commonly observed (9,10).

The mutation rate of SF3B1 in breast cancer generally ranges from 2% to 4%. In TNBC, novel somatic mutations, including those in SF3B1, have been identified. Because phosphoglycerate dehydrogenase (PHGDH), which is involved in the first stages of L-serine production, is downregulated as a result of mis-splicing, SF3B1 has been shown to enhance sensitivity to low serine circumstances (11). This is consistent with TNBC's ability to upregulate PHGDH in some situations and its reliance on serine synthesis signaling. However, there is no definitive explanation for the relationship between SF3B1 mutations and TNBC in the serine synthesis pathway. SF3B1 knockdown results in suppressed proliferation, migration, and invasion of TNBC cells and increases apoptosis in these cell lines (12). Because chemoresistance is often found in TNBC in Bali, we aimed to study this particular breast cancer population. Therefore, this study aimed to assess the association between SF3B1 expression and chemoresistance status in TNBC and the risk of chemoresistance among TNBC patients with high SF3B1 expression

Materials and Methods

Study design

This study is a case-control study. This research occurred at Prof. Dr. I.G.N.G. Ngoerah General Hospital Denpasar and the Integrated Biomedical Laboratory, Faculty of Medicine, Udayana University from March 2021 to October 2021. This study has received ethical clearance from the Faculty of Medicine, Udayana University Research Ethic Committee No 1848/UN14/2/2/VII/14/LT/2021.

Samples

The samples in this study were stage III breast cancer patients with the TNBC subtype who received neoadjuvant

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chemotherapy and were registered in the oncology division of the surgical department at Prof. Dr. I.G.N.G. Ngoerah General Hospital in 2015-2020. The inclusion criteria in this study were: 1) stage III TNBC patients who had undergone neoadjuvant chemotherapy using a complete three-series of anthracycline and taxane-based chemotherapy regimens and had complete records in the medical record (13), and 2) biopsy or resection tissue samples that had been stored in the pathology anatomy department, Faculty of medicine, Udayana University, as recorded in the medical record.

Exclusion criteria in this study include: 1) having a history of other malignancies unless deemed disease-free for five years or more, as recorded in the medical record, 2) patients who had breast cancer during pregnancy or became pregnant during therapy as recorded in the medical record, 3) Patients with recurrent breast cancer, 4) Incomplete medical records, 5) Tissue samples that are damaged or unsuitable for staining.

Variables and measurement

This study evaluated the following variables: SF3B1 expression, neoadjuvant chemotherapy (NAC) response, histology grading, menopausal status, Ki-67, TIL, and LVI. The variables NAC response, menopausal status, TIL expression, and LVI were obtained from medical records. Meanwhile, SF3B1 and Ki-67 expression variables were obtained from the IHC examination. The NAC response will then be grouped into partial response and no response.

Immunohistochemistry (IHC)

IHC examination of SF3B1 expression was evaluated using the standard avidin-biotin method using anti-SF3B1 rabbit polyclonal antibody (PA5-41723 Thermo Fisher Scientific U.S., diluted 1:1,000). Following xylene deparaffinization, the preparations were rehydrated with 100%, 95%, and 70% alcohol, respectively, for two minutes each, followed by one minute for 70% alcohol and one minute for water. In a pressure cooker, antigen retrieval was performed for 10 minutes in 10 mM citrate buffer at pH 6.0. After cooling to room temperature, PBS was used to wash the preparation. Then, blocking was carried out with 3% H_2O_2 for 15 minutes, followed by blocking endogenous biotin with the Dako Cytomation Biotin Blocking System (#X0590 Agilent, U.S.). The preparations were then incubated with 10% goat serum for 1 hour and incubated with primary antibodies overnight at 40 °C. A biotinylated secondary antibody (#BA-1000, Vector Laboratories, U.S.) was used to identify the interaction between the primary antibody and the antigen. Streptavidin-HRP (Dako #K1016, Agilent, U.S.) was then administered. The Dako Liquid DAB + Substrate-Chromogen System (K3468, Agilent, U.S.) measured immunoreactivity.

Statistical analysis

Version 20.0 of SPSS for Windows was used to analyze the data. The statistical analysis was conducted using logistic regression for multivariate analysis, chi-square for bivariate analysis, and univariate analysis. The p-value is considered significant if $p \leq 0.05$.

Results

This study aims to determine the relationship between SF3B1 expression and the response to NAC in TNBC patients. So far, this research has completed several stages. Because this research uses samples of stored biological material, the basic characteristics data of the samples have been obtained and described univariately, as seen in Table 1. Age and age at diagnosis were normally distributed ($p > 0.05$) and matched between case and control groups.

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Table 1. Baseline characteristics

Variables	Sample (N=60)	
	n	%
Age (mean±SD)	51.28 ± 10.765	
Age at diagnosis (mean±SD)	50.52 ± 10.882	
Parity n (%)		
0	6	10%
>=1	54	90%
Tumor location n (%)		
Mammae Dextra	36	60%
Mammae Sinistra	24	40%
Quadrant n (%)		
Central	28	46.8%
Upper Inner	5	8.3%
Lower Inner	3	5%
Upper Outer	11	18.3%
Lower Outer	8	13.3%
Overlapping Site	2	3.3%
Unspecified	3	5%
Tumor stage n (%)		
T1	2	3.3%
T2	7	11.7%
T3	15	25%
T4	36	60%
Nodal stage n (%)		
N0	14	23.3%
N1	19	31.7%
N2	25	41.7%
N3	2	3.3%
Distant metastasis n (%)		
Non-Metastasis	44	73.3%
Metastasis	16	26.7%
Karnofsky score n (%)		
80	14	23.3%
90	28	46.7%
100	18	30%
Menstrual status n (%)		
Pre-Menopause	23	38.3%
Post-Menopause	37	61.7%
Stage n (%)		
Early stage	10	16.7%
Late stage	50	83.3%
Histological grade n (%)		
Well-differentiated	43	71.7%
Poorly differentiated	17	28.3%
Ki67 n (%)		
Low	35	58.3%
High	25	41.7%

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The bivariate analysis's findings demonstrated that SF3B1 status, TIL, and Ki-67 were all substantially linked to a higher likelihood of chemoresistance in TNBC-type breast cancer. High Ki-67 levels increased the risk of chemoresistance by 6.4 times compared to low Ki-67 levels (95% CI: 1.20-34.19; p= 0.017). Meanwhile, high TIL was associated with a 4.8 times (95% CI: 1.05-21.75; p= 0.031). On the other hand, high SF3B1 expression increased the risk of chemoresistance by 13.5 times compared to patients with low SF3B1 expression (95% CI: 1.56-116.24; p= 0.008). No significant relationship was found between the variables of age, grading, and menopausal status (Table 2).

Table 2. Results of bivariate analysis between chemoresistance status (partial response and no response) to several clinicopathological variables and SF3B1.

Variables	Response to NAC		OR	95%CI	p
	No Response (Case)	Partial Response (Control)			
Age					
> 40 years old	7 (11.7%)	38 (63.3%)	1.1	0.22-6.58	0.835
≤ 40 years old	2 (3.3%)	13 (21.7%)			
Grade					
Poorly differentiated	5 (8.3%)	12 (20%)	4	0.93-17.58	0.049
Well-differentiated	4 (6.7%)	39 (65%)			
Menstrual status					
Pre-menopause	2 (3.3%)	21 (35%)	2.4	0.46-12.98	0.281
Post-menopause	7 (11.7%)	30 (50%)			
Ki-67					
High (>20%)	7 (11.7%)	18 (30%)	6.4	1.20-34.19	0.017*
Low (≤ 20%)	2 (3.3%)	33 (55%)			
TIL					
High	6 (10%)	15 (25%)	4.8	1.05-21.75	0.031*
Low	3 (5%)	36 (60%)			
SF3B1 Status					
High (>30%)	8 (13.3%)	19 (31.7%)	13.5	1.56-116.24	0.008*
Low (≤ 30%)	1 (1.7%)	32 (53.5%)			

*Analysis was conducted using the chi-square test. Results were considered significant if p-value ≤ 0.05.

Multivariate analysis was carried out to test whether the relationship between variables obtained in bivariate analysis were independent. At this stage, Ki-67, TIL, and SF3B1 were included in the analyzed variables. The results of the multivariate analysis found that the three variables were independently associated with chemoresistance in TNBC-subtype breast cancer. SF3B1 still has a significant effect with an adjusted OR of 13.5 (95% CI: 1.56-116.24; p=0.018). On the other hand, Ki-67 and TIL

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were also found to independently influence chemoresistance with adjusted OR of 14.4 (95% CI: 1.80-115.73; p = 0.012) and 6.7 (95% CI: 1.12-40.46; p = 0.037) (Table 3).

Table 3. Multivariate logistic regression analysis between NACT response with SF3B1, Ki-67, and TIL.

Variables	B	Adj (OR)	95%CI	p
SF3B1	2.601	13.5	1.56-116.24	0.018*
Ki-67	2.671	14.4	1.80-115.73	0.012*
TIL	1.908	6.7	1.12-40.46	0.037*
Constant	-4.944	0.007	-	0.000

*p< 0.05

Discussion

This study aimed to assess the association between SF3B1 expression and chemoresistance status in TNBC and the risk of chemoresistance among TNBC patients with high SF3B1 expression. According to our study we found that the SF3B1 status, TIL, and Ki-67 were all substantially linked to a higher likelihood of chemoresistance in TNBC-subtype breast cancer. High Ki-67 levels increased the risk of chemoresistance by 6.4 times compared to low Ki-67 levels (95% CI: 1.20-34.19; p= 0.017). Meanwhile, high TIL was associated with 4.8 times (95% CI: 1.05-21.75; p= 0.031). On the other hand, high SF3B1 expression increased the risk of chemoresistance by 13.5 times compared to patients with low SF3B1 expression (95% CI: 1.56-116.24; p= 0.008).

Splicing factors are essential to components of the spliceosome responsible for accurately and efficiently removing introns from pre-mRNA to produce mature mRNA. Abnormal splicing, often caused by dysregulated expression of splicing factors, is associated with various types of cancer (10). These irregularities can influence cancer progression, response to treatment, and patient prognosis (13). The role of splicing factors in modulating response to NAC is a growing area of research, especially in cancers such as breast cancer, where NAC is frequently used (14). The largest member of the SF3B complex, splicing factor 3b subunit 1 (SF3B1), is the primary constituent of the U2-type small nuclear ribonucleoprotein (snRNP), the primary spliceosome involved in the splicing of precursor mRNA (pre-mRNA) (15).

This study found a significant relationship between increased SF3B1 expression and NAC therapy response in TNBC patients with increased risk of chemoresistance among patients with high SF3B1 expression (no response vs. partial response). However, no other study was ever conducted to assess the association between SF3B1 expression with the therapeutic response; according to in vitro research conducted by Zhang et al. using MDA-MB-231 cell line showed that the knockdown of SF3B1 was shown to suppress proliferation, migration, and invasion of TNBC cells and increases the incidence of apoptosis in this cell line (12). Although it does not provide a direct association regarding how SF3B1 overexpression affects the outcome of NAC therapy, this study provided insight into the potential effect of decreased SF3B1 expression and activity toward the therapeutic response in TNBC patients and also how the effect of its increased expression.

From a physiological perspective, SF3B1 is crucial for early spliceosome assembly and branch site identification. The hydrophilic N-terminal region of SF3B1 has several U2AF2 binding motifs that help localize U2 snRNP close to the branch site (16). Phosphatidylinositol 3-kinase (PI3K) target of rapamycin 1, Huntingtin, elongation factor 3, and a subunit of protein phosphatase 2A comprise the 22 nonidentical HEAT repeats the make up two-thirds of the C terminus. These repeats will subsequently form a helical

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stem structure that facilitates interaction with other SF3B subunits (17).

In TNBC, one of the novel somatic mutations discovered also includes a mutation in SF3B1. According to reports, SF3B1 increases susceptibility to low serine conditions brought on by mis-placing, which results in the downregulation of phosphoglycerate dehydrogenase (PHGDH), an enzyme involved in the first step of L-serine production. This is in line with the characteristics of TNBC, which relies on serine synthesis signaling, and in some cases, TNBC can amplify PHGDH. However, there has been no definite explanation regarding the relationship between SF3B1 mutations and TNBC in the serine synthesis pathway (18).

Although the exact mechanism by which overexpression of SF3B1 affects the response to NAC therapy in TNBC patients is not fully understood, several theories have been proposed to explain the pathways involved in this mechanism. The response to NAC involves various aspects such as gene expression and protein isoform production, regulation of apoptosis, DNA repair, and tumor microenvironment (17, 19).

Overexpression of splicing factors can change the splicing pattern of certain genes, resulting in different protein isoforms. These isoforms may have different or even conflicting functions, which may affect the survival of cancer cells during chemotherapy. For example, splicing of BCL-2 family genes can produce pro-apoptotic and anti-apoptotic isoforms, affecting the balance between cell life and death during treatment (20). In addition, splicing factors can influence the splicing of genes involved in the apoptotic pathway, where changes in the balance of pro-apoptotic and anti-apoptotic isoforms can determine the sensitivity of cancer cells to chemotherapeutic agents. For example, SF3B1 and SRSF1 can modulate the splicing of apoptosis regulators, affecting the effectiveness of NAC (21, 22). Some splicing factors also influence the splicing of genes involved in DNA repair pathways, which are critical for cell survival after DNA-damaging chemotherapy (23). In addition, splicing factors can regulate the expression of genes involved in the tumor microenvironment, including those involved in angiogenesis, immune response, and extracellular matrix remodelling. These changes may influence the overall response to chemotherapy by altering the structural and functional environment of the tumor (24).

This study has several limitations. First, the case-control research design has weaknesses, such as the possibility of selection bias and information bias. Second, the relatively small sample size may limit the ability to detect statistically significant relationships and reduce the reliability of the study findings. Third, using retrospective data from patient medical records can cause problems such as incomplete or inaccurate data. Additionally, the variables analyzed may not include all factors influencing response to NAC, so other unmeasured factors may also play a role. Evaluation of SF3B1 and Ki-67 expression using IHC methods may also be subject to inter-rater variation, affecting the consistency and reliability of the results. Furthermore, the results of this study may not be generalizable to all populations of TNBC patient populations, as it was conducted in only one hospital. Hence, it needs to be validated with larger studies and more diverse populations. Lastly, this study did not evaluate patient survival prognosis based on SF3B1, Ki-67, and TIL expression after NAC therapy, so a comprehensive survival analysis is needed to understand better the long-term impact of these factors on patient clinical outcomes.

SF3B1 expression is significantly associated with NACT response in stage III TNBC, alongside high Ki-67 and TIL levels. These findings suggest that SF3B1 plays a chemoresistance role, indicating its potential as a therapeutic target to improve neoadjuvant chemotherapy responses in TNBC patients. Future research should focus on developing therapies targeting SF3B1 to overcome chemoresistance in TNBC. Clinical trials evaluating the efficacy of SF3B1 inhibitors, in combination with standard chemotherapy

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regimens, could provide valuable insights into improving treatment outcomes for TNBC patients.

Ethical Consideration

This study has been approved by the ethical commission of the Faculty of Medicine Udayana University, with letter number 1848/UN14.2.2.VII.14/LT/2021 issued on July 13th, 2021. We obtained informed consent from all subjects included in this study.

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Conflict of Interest

All authors stated no conflict of interest regarding this research.

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