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[1]Department of Surgery Faculty of Medicine Universitas Sumatera Utara
[2]Division of Surgical Oncology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara
[3]Department of Community Medicine and Preventive Medicine, Faculty of Medicine, Universitas Sumatera Utara

Corresponding author: Dedy Hermansyah. Division of Surgical Oncology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara. E-mail: dedi.hermansyah@usu.ac.id. ORCID ID: http//www.orcid.org/0000-0002-5980-2556.

The Relationship Between KI67 Expression and Grading with Chemotherapy Response in Triple-Negative Breast Cancer Patients at Haji Adam Malik General Hospital, Medan

Edy Anugrah Putra[1], Dedy Hermansyah[2], Endi Taris Pasaribu[2], Putri Chairani Eyanoer[3]

ABSTRACT

Background: The response to chemotherapy in TNBC varies greatly, highlighting the need for predictive factors to estimate the success of the therapy. **Objective:** The primary aim of this study is to analyze the relationship between Ki67 expression and clinicopathological features with chemotherapy response in locally advanced TNBC. **Methods:** This retrospective study utilized secondary data from the medical records of locally advanced TNBC patients at Haji Adam Malik General Hospital, Medan. Out of an initial sample of 50 patients, 35 met the inclusion criteria, which required a confirmed TNBC diagnosis through histopathological and immunohistochemical examination, as well as complete clinical data. Chemotherapy response was assessed based on the World Health Organization (WHO) criteria, ensuring a standardized evaluation of treatment outcomes. **Results:** The majority of patients were aged ≥50 years (54.5%), with a dominant tumor size of 2–5 cm (69.7%) and high histological grading (Grade 3: 60.6%). A total of 45.5% of patients exhibited high Ki67 expression (≥30%). Chemotherapy response was categorized as complete response (12.1%), partial response (45.5%), stable disease (30.3%), and progressive disease (12.1%). Statistical analysis revealed a significant relationship between Ki67 expression and chemotherapy response (p=0.02), with patients exhibiting high Ki67 expression more frequently achieving complete or partial response. **Conclusion:** High Ki67 expression is a critical indicator for predicting chemotherapy response in TNBC. Integrating Ki67 assessment with other clinicopathological factors is highly recommended to enhance predictive accuracy and optimize therapeutic planning for more effective treatment outcomes.

Keywords: chemotherapy response, histological grading, Ki67, Triple Negative Breast Cancer

1. BACKGROUND

Breast tumors are the most common neoplasm in women (1). The American Cancer Society (ACS) estimates that breast cancer accounts for 30% of all new female cancer cases each year (1). According to the Global Cancer Observatory's 2022 data, breast cancer is the most frequently diagnosed cancer among Indonesian women, with an age-standardized incidence rate of 41.8 per 100,000 women (2). It also ranks as the leading cause of cancer-related deaths in women, with an age-standardized mortality rate of 15.7 per 100,000. In 2022, Indonesia reported approximately 66,271 new breast cancer cases, accounting for 16.2% of all cancer cases in the country (2). The same year saw about 22,598 deaths attributed to breast cancer, representing 9.3% of all cancer-related deaths (2).

Breast cancer is a complex condition with various subtypes that can be classified based on several criteria, including histological type, hormone status, and protein expression (3). Understanding these classifications is crucial for determining prognosis, treatment strategies, and appropriate clinical management approaches (4). Triple-negative breast cancer (TNBC) is immunohistochemically defined by the absence of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER-

2) (5). Locally advanced breast cancer refers to breast malignancies that are inoperable without distant metastasis (6). This stage accounts for 15–20% of breast cancer cases and is characterized as a molecularly heterogeneous disease, often demonstrating aggressive clinical behavior and higher prevalence among younger women (7). Once TNBC metastasizes, it is associated with the poorest prognosis and the shortest overall survival (OS) among all breast cancer subtypes (8). Clinical response to chemotherapy is observed in 40–50% of TNBC patients (9). With advancements in neoadjuvant chemotherapy (NACT) regimens and newer chemotherapeutic agents, patients have shown positive responses (approximately 80%), with complete pathological responses observed in 6–32.9% of cases (9).

Ki67 is a nuclear protein that plays a critical role in regulating cell proliferation and is widely used as a proliferation marker in various cancers, including TNBC (10). In locally advanced TNBC, high Ki67 expression is generally associated with an increased rate of cancer cell proliferation (11). Elevated Ki67 levels are often considered an indicator of tumor aggressiveness, correlating with a higher risk of metastasis and local recurrence following primary therapies, such as chemotherapy or radiotherapy (10, 12). The role of Ki67 in locally advanced TNBC is also linked to treatment response (13). Several studies have shown that patients with high Ki67 levels tend to respond better to neoadjuvant chemotherapy (13). This is because highly proliferative cells are more susceptible to the cytotoxic effects of chemotherapy. However, high Ki67 expression is also often associated with poor prognosis, especially if the tumor does not respond well to therapy (12, 14).

Factors influencing chemotherapy response are highly variable and include genetic, biological, and clinical aspects of the patient. One of the key factors is the molecular characteristics of the tumor itself, such as hormone receptor expression, HER2 status, and cell proliferation measured using markers like Ki67 (3, 4). Tumors with high proliferation rates or positive HER2 expression tend to respond better to certain chemotherapies, particularly in breast cancer (3). Additionally, the presence of genetic mutations or epigenetic changes in cancer cells can influence the tumor's sensitivity or resistance to the chemotherapy drugs used (15).

Nevertheless, the use of Ki67 as a prognostic predictor in TNBC remains controversial. Some studies suggest specific thresholds for Ki67 that could help predict therapy outcomes and long-term prognosis in TNBC patients, but no definitive consensus has been reached (16, 17). As a result, Ki67 is more commonly used in conjunction with other markers to enhance clinical evaluation and guide therapeutic decision-making (18).

2. OBJECTIVE

The primary aim of this study is to analyze the relationship between Ki67 expression and clinicopathological features with chemotherapy response in locally advanced TNBC.

material and methods

Materials and study design

This study is an observational analytic research with a cross-sectional design conducted at Haji Adam Malik General Hospital, Medan, Indonesia. The study was conducted in adherence to ethical standards, with approval obtained from the Ethics Committee of Universitas Sumatera Utara. Patient confidentiality and data privacy were maintained throughout the study. Data collection took place from October 2023 to 2024. The study population included all patients diagnosed with locally advanced triple-negative breast cancer (TNBC) at Haji Adam Malik General Hospital during the study period.

Methods

Samples were selected using a consecutive sampling method, including all subjects who met the inclusion and exclusion criteria until the required sample size was achieved. The minimum sample size, calculated using the Lemeshow formula, was determined to be 34 patients (19). This study used Ki67 and clinicopathology score as a dependent variable with chemotherapy response to locally advanced TNBC as an independent variable.

Statistical analysis

Analysis was carried out descriptively. The obtained data are presented with their frequency and percentage. Subsequently, p-values are calculated to assess the accuracy of the results.

3. RESULTS

This study analyzes 35 patients with locally advanced TNBC who were treated at Haji Adam Malik General Hospital, Medan, North Sumatra, Indonesia. Among the total patients, 54.5% were aged ≥50 years, while 45.5% were aged <50 years. All patients were female, reflecting the predominance of breast cancer in women. The findings indicate that TNBC affects both younger and older age groups, with a slight predominance in the older age group in this cohort (Table 1).

Clinicopathological analysis revealed that the majority of patients (69.7%) had tumors measuring 2–5 cm, indi-

Variable	Frequency	Percentage (%)
Age		
<50	15	45.5
≥50	20	54.5
T (tumor size)		
T1	5	15.2
T2	25	69.7
T3	5	15.2
N (nodul)		
N0	22	60.6
N1	8	24.2
N2	5	15.2
Ki67		
<30%	18	51.42
>30%	17	48.58
Chemotherapy Response		
Complete Response	4	12.1
Partial Response	17	45.5
Stable Disease	10	30.3
Progressive Disease	4	12.1
Total	35	100.0

Table 1. Demographic characteristics

Histological Grading	Complete/Partial Response (CR/PR)	Stable/Progressive Disease (SD/PD)	p-value
Grade1+2	8	6	0.03*
Grade 3	13	8	

Table 2. Clinicopathology relationship with chemotherapy response

KI67 expression	Complete/Partial Response (CR/PR)	Stable/Progressive Disease (SD/PD)	p-value
<30%	8	10	0.02*
≥30%	12	5	

Tabel 3. Ki-67 relationship with chemotherapy response

cating locally advanced stages. Tumors larger than 5 cm or smaller than 2 cm were found in 15.2% of patients, respectively. Based on histological grading, most tumors were classified as Grade 3 (60.6%), reflecting a high level of tumor aggressiveness. Grade 1 and Grade 2 tumors were less frequently observed, at 9.1% and 30.3%, respectively. Evaluation of lymph node status showed that 60.6% of patients were categorized as N0 (no lymph node involvement), while 24.2% and 15.2% had N1 and N2 involvement, respectively, indicating varying degrees of local spread.

Analysis revealed that 51.42% of patients had Ki67 levels below 30%, while 48.58% exhibited Ki67 levels of 30% or higher. These findings align with the aggressive nature of TNBC, where higher Ki67 levels are associated with increased proliferation rates. Patients with higher Ki67 expression often display more advanced tumor characteristics and are more likely to respond to chemotherapy.

Chemotherapy response was evaluated using the WHO criteria. Partial response (PR) was observed in 45.5% of patients, making it the most common outcome, while complete response (CR) was seen in 12.1% of patients. Stable disease (SD), characterized by no significant changes in tumor size or progression, was observed in 30.3% of patients. Progressive disease (PD), indicating tumor growth despite chemotherapy, occurred in 12.1% of cases. These findings highlight the variability of TNBC responses to chemotherapy, with a significant proportion of patients showing varying levels of sensitivity to treatment.

The relationship between histological grading and chemotherapy response showed a significant correlation. Patients with Grade 3 tumors had a higher likelihood of achieving partial or complete response compared to those with low-grade tumors ($p = 0.03$). This correlation reinforces the aggressive nature of high-grade tumors, which, despite being biologically more active, tend to respond better to cytotoxic agents. In contrast, patients with low-grade tumors showed a higher incidence of stable or progressive disease, indicating lower sensitivity to chemotherapy.

Ki67 expression also had a significant association with chemotherapy response ($p = 0.02$). Patients with Ki67 levels ≥30% were more likely to achieve partial or complete response compared to those with Ki67 levels <30%. This finding highlights the predictive value of Ki67 as a marker of chemotherapy sensitivity in TNBC. Tumors with high Ki67 levels are characterized by rapid cell division, making them more susceptible to the effects of chemotherapy. Conversely, patients with low Ki67 levels more frequently experienced stable or progressive disease, suggesting less aggressive tumor biology but potentially lower chemotherapy sensitivity.

This study emphasizes the importance of clinicopathological manifestations, particularly histological grading and Ki67 expression, in predicting chemotherapy response in TNBC. Tumors with high grading and elevated Ki67 levels are more likely to exhibit a positive response to chemotherapy, reflecting higher proliferative activity to cytotoxic agents. The variability in responses highlights the heterogeneity of TNBC and the need for a personalized treatment approach based on the specific characteristics of the tumor.

4. DISCUSSION

This study examines the relationship between Ki67 expression, clinicopathological characteristics, and chemotherapy response in patients with locally advanced TNBC. The findings reveal a significant correlation, providing valuable insights into predictive markers for therapy response and the aggressive nature of TNBC. The age distribution of patients shows a slight predominance in the ≥50 years age group (54.5%), though younger patients (<50 years) also represent a substantial proportion (45.5%). This aligns with the global and regional epidemiology of TNBC, where younger women in developing countries like Indonesia are more susceptible to TNBC due to genetic predispositions and environmental factors (20, 21). These findings are consistent with Ma et al. (2022), who reported that TNBC is more common among younger women in developing regions compared to high-income areas (22). This distribution underscores the importance of tailored screening and management strategies for different age groups.

The majority of tumors in this study measured 2–5 cm (69.7%) and were classified as Grade 3 histologically (60.6%), reflecting the aggressive nature of TNBC. Most patients (60.6%) did not exhibit lymph node involvement (N0), despite TNBC's known biological aggressiveness. This suggests that localized spread of TNBC can precede extensive lymphatic involvement in some cases. Clinically, these findings underscore the importance of early detection before lymph node metastasis, which can significantly worsen the prognosis. These results are consistent with the findings of Bendardaf et al. (2020), who reported that Grade 3 tumors are most commonly observed in TNBC due to their high proliferative capacity and molecular heterogeneity (23).

A total of 48.58% of patients exhibited high Ki67 expression (≥30%), reflecting the aggressive biology of the tumor. High Ki67 expression was significantly correlated with better chemotherapy response ($p = 0.02$), consistent with Dowsett et al. (2022), who stated that tumors with rapid proliferation are more vulnerable to cytotoxic agents (18). Chemotherapy responses varied, with partial response (PR) in 45.5% of patients, complete response (CR) in 12.1%, and stable or progressive

disease (SD/PD) in 42.4%. The correlation between high histological grade and better chemotherapy response (p = 0.03) reinforces the idea that biologically aggressive tumors are more likely to respond to cytotoxic therapy (24). However, the presence of SD/PD in 42.4% of patients indicates TNBC heterogeneity and the possibility of intrinsic chemotherapy resistance.

Like other studies, this research has some limitations that should be considered when interpreting the results. The cross-sectional design only allows for observation of the relationship between variables at a single point in time. As such, the study cannot evaluate causal relationships or the dynamics of Ki67 expression changes and chemotherapy responses over time. This study focused solely on histological grading and Ki67 expression without considering other molecular factors, such as p53 mutations, BRCA1/2, or additional biomarkers like tumor-infiltrating lymphocytes (TILs).

5. CONCLUSION

These factors could provide deeper insights into chemotherapy response in TNBC. Additionally, Ki67 expression was assessed using immunohistochemical techniques, which may be influenced by variability between laboratories, including the type of antibodies used and interpretation techniques. This variability could affect the consistency of the results.

- **Author's contribution**: Conceptualization, supervision, and validation: EDP; Methodology, formal analysis, and data curation: EDP and PCE; Writing original draft, analysis, and visualization: EDP, DH, and ETP; Review draft and project administration: DH.
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