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Correlation between Estrogen Receptor, Progesterone Receptor, and Ki-67 Expression Levels with Neoadjuvant AC-T Chemotherapy Response in Triple Positive Breast Cancer (TPBC) Patients after Modified Radical Mastectomy (MRM) at Prof. Dr. I.G.N.G. Ngoerah General Hospital

Ni Made Apriliani Saniti[1*], Ida Bagus Made Suryawisesa[2], I Wayan Sudarsa[2]

[1]Department of General Surgery, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Denpasar, Indonesia (80113)

[2]Division of Oncology, Department of Surgery, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Denpasar, Indonesia (80113)

E-mail: apriliani.saniti@gmail.com; gusdeck2001@yahoo.com; sudarsa1510@yahoo.com

*Corresponding author details: Ni Made Apriliani Saniti; apriliani.saniti@gmail.com

ABSTRACT

Background: Triple Positive Breast Cancer (TPBC), a subtype of breast cancer expressing ER, PR, and HER-2, has unique biological characteristics that influence therapy response. Neoadjuvant AC-T chemotherapy is commonly used for TPBC; however, the correlation between ER, PR, and Ki-67 expression levels and therapy response remains unclear. TPBC has a lower pathological complete response (pCR) rate compared to other subtypes, but a low pCR does not always indicate a poor prognosis. This study aimed to evaluate the correlation between ER, PR, and Ki-67 expression levels and the response to neoadjuvant AC-T chemotherapy in TPBC patients to support more effective and safer treatment strategies. ***Methods:*** This analytical observational study used a cross-sectional design conducted at Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, from June 2022 to June 2023. The target population was TPBC patients who underwent neoadjuvant AC-T chemotherapy and MRM surgery. Samples were collected using consecutive sampling. Data were analyzed using descriptive statistics, ROC curve analysis to determine variable cut-off points, and Chi-Square tests to assess relationships between variables. ***Results:*** ROC analysis showed a cut-off point for ER at 17.5% (AUC 0.506, p=0.950), PR at 25% (AUC 0.521, p=0.815), and Ki-67 at 35% (AUC 0.465, p=0.700). Chi-square tests revealed no significant correlation between high expression of ER (p=0.717), PR (p=0.505), or Ki-67 (p=0.970) and chemotherapy response. ***Conclusions:*** ER, PR, and Ki-67 expression levels do not significantly correlate with the response to neoadjuvant AC-T chemotherapy in TPBC patients.

Keywords: triple positive breast cancer; neoadjuvant chemotherapy; AC-T; estrogen receptor expression; progesterone receptor expression; Ki-67; therapy response.

INTRODUCTION

Breast cancer remains a significant global health issue due to the increasing number of new cases and the high rates of morbidity and mortality. As research in breast cancer advances, a deeper understanding of the nature and characteristics of each cancer cell type is emerging. This progress is expected to enhance patient management and reduce both morbidity and mortality among those affected. According to WHO 2020, breast cancer accounted for 11.7% (2,261,419) of all new cancer cases worldwide, making it the most commonly diagnosed cancer. It was also the fourth leading cause of cancer-related deaths globally. In Indonesia, breast cancer represented the highest number of new cancer cases at 16.6% (65,858) and was the leading cause of cancer-related deaths among women at 9.6% (222,430) [1].

Breast cancer is a heterogeneous disease, characterized by a diversity of genotypes and phenotypes. It is classified into several subtypes based on the expression of specific receptors, including hormonal receptors (HR) and the human epidermal growth factor receptor 2 (HER-2). The presence of estrogen and/or progesterone receptors is referred to as hormone receptor-positive (HR+), while their absence denotes hormone receptor-negative (HR-). HR+ cancers can be treated with hormonal therapy to reduce estrogen levels or block estrogen receptors, and they tend to grow more slowly than HR-cancers.

In addition to hormonal status, HER-2 status is also evaluated, as HER-2-positive breast cancers tend to grow and spread more rapidly but respond better to chemotherapy [2].

HER-2 protein expression is reported in 15-20% of breast cancers and is associated with decreased disease-free survival and overall survival. Approximately half of HER-2-expressing breast cancers are also HR+, and about 10% of HR+ breast cancers also express HER-2 [3]. In addition to ER, PR, and HER-2 expression levels, Ki-67 is assessed during immunohistochemical examination. High Ki-67 levels are generally observed in breast cancer and are associated with poorer patient outcomes [4]. HR-positive breast cancers with high Ki-67 levels have a worse prognosis, although they may respond well to certain chemotherapies [5].

Triple Positive Breast Cancer (TPBC) is a subtype that expresses ER, PR, and HER-2, accounting for about 10% of all breast cancer cases [6]. TPBC requires special attention due to its distinct clinical and biological characteristics, which affect its treatment and prognosis [7]. Chemotherapy combined with anti-HER-2 agents is the main treatment for HER-2-positive breast cancer, regardless of hormone receptor status.[8] However, hormone receptor status may reduce chemotherapy sensitivity. For TPBC patients, the combination of trastuzumab and endocrine therapy has shown promising results, especially in early-stage cases [8–10].

Neoadjuvant chemotherapy is a common treatment modality for breast cancer, initially used for locally advanced cases. It is now frequently used for operable patients, with anthracycline, cyclophosphamide, and taxane (AC-T) being the most common regimens [11–13]. However, advanced clinical stages, poor histological grading, and ER/PR positivity are predictive factors for cancer progression during anthracycline/cyclophosphamide chemotherapy with or without taxane [13].

Due to the lack of clarity regarding the relationship between ER, PR, and Ki-67 expression levels and the neoadjuvant chemotherapy response, particularly the AC-T regimen in TPBC patients, researchers are interested in exploring this further. This could enable clinicians to provide more effective and safe management for breast cancer patients, especially those with TPBC.

METHOD

This analytical observational study employed a cross-sectional design conducted at Prof. Dr. I.G.N.G. Ngoerah General Hospital in Denpasar, Indonesia. The target population comprised patients diagnosed with TPBC who underwent neoadjuvant chemotherapy with the AC-T regimen followed by modified radical mastectomy (MRM).

Ethical clearance for this study was issued by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Udayana, Indonesia (ethical clearance number 2070/UN14.2.2.VII.14/LT/2023).

The research was carried out at the Surgical Outpatient Clinic and the Surgical Ward of Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, over a period spanning from June 2022 to June 2023. Samples were collected using a consecutive sampling method. The sample population was determined based on inclusion and exclusion criteria derived from medical records, employing a consecutive sampling method. The minimum sample size was calculated using the formula for estimating a single proportion, resulting in a required sample size of approximately 35 participants. Inclusion Criteria: Patients diagnosed with TPBC exhibiting HER-2 positivity (3+), those who had received neoadjuvant chemotherapy with the AC-T regimen, and patients with complete medical records detailing patient data, anamnesis, physical examinations, supportive investigations, chemotherapy regimens, and therapeutic responses. Exclusion Criteria: Patients with other malignancies (e.g., ovarian, liver, lung cancers), incomplete medical records regarding histopathology, oestrogen, and progesterone receptor levels, and Ki-67, as well as those suffering from chronic, systemic, or autoimmune diseases. Additionally, patients diagnosed with stage IV TPBC at the time of initial diagnosis were excluded.

The oestrogen receptor (ER) status was determined through immunohistochemical analysis of biopsy samples, classified according to the Allred scoring system. The analysis of progesterone receptors (PR) followed a similar methodology. Ki-67, a marker of cell proliferation, was assessed via immunohistochemistry on paraffin-embedded tissue blocks. The responses to neoadjuvant chemotherapy were categorised as follows: pathological complete response (pCR), clinical complete response (cCR), and partial response, based on established clinical and radiographic criteria. Negative responses were defined as stable disease or progressive disease, with histological grading assessed through histopathological examination. Immunohistochemical assessments were performed to evaluate the expression levels of ER, PR, and Ki-67, with the resulting data subjected to statistical analysis.

Collected data on patient characteristics and examination results were documented and entered into the Statistical Package for Social Sciences (SPSS) software. Data were analysed using descriptive statistics to summarise patient characteristics. Receiver Operating Characteristic (ROC) curve analysis was employed to determine optimal cut-off points for ER, PR, and Ki-67 in relation to the response to neoadjuvant chemotherapy. Additionally, Chi-Square tests were utilised to assess relationships between the variables.

RESULTS

This study involved 85 subjects, specifically patients with Triple Positive Breast Cancer (TPBC) undergoing neoadjuvant chemotherapy with the AC-T regimen.

The characteristics of the respondents were described based on age, histopathological type of surgery, grading, menstrual status, and age at menarche. The data is presented in Table 1.

TABLE 1: The General Characteristics of Subjects.

Characteristic	Neoadjuvant AC-T Response		p-value
	Negative Response (n=12)	Positive Response (n=73)	
Age (year)	48,08±9,9	49,7±9,3	0,571*
Age at Menarche (years)	13,5±1,3	13,6±1,4	0,916*
Stage			
- Stage IIIA	1 (1,2%)	26 (30,6%)	0,107**
- Stage IIIB	11 (12,9%)	44 (51,8%)	
- Stage IIIC	0 (0%)	3 (3,5%)	
Menstrual Status			
- Post Menopause	6 (7,1%)	34 (40%)	0,826**
- Premenopause	6 (7,1%)	39 (45,9%)	
Histopathological Type			
- Invasive Carcinoma NOS	11 (12,9%)	55 (64,7%)	0,420**
- Invasive Lobular Carcinoma	0 (0%)	11 (12,9%)	
- Special Type Carcinoma	0 (0%)	4 (4,7%)	
- Infiltrative Duct Carcinoma	1 (1,2%)	2 (2,4%)	
- Infiltrative Duct Carcinoma	0 (0%)	1 (1,2%)	
Grade			
- Grade I	0 (0%)	1 (1,2%)	0,614**
- Grade II	4 (4,7%)	34 (40%)	
- Grade III	8 (9,4%)	38 (44,7%)	

Note: *Independent t-test, ** Chi-Square.

Table 1 illustrates the characteristics of the research subjects. The average age in the negative response group to neoadjuvant AC-T chemotherapy was 48.08 years (SD: 9.9), while the positive response group had an average age of 49.7 years (SD: 9.3), with a p-value of 0.571 (>0.05), indicating no significant difference in age between the negative and positive chemotherapy responses. The age at menarche was similar across both groups, with values of 13.5 years and 13.6 years, respectively, and a p-value of 0.916 (>0.05), indicating no significant difference.

Regarding the stage of cancer, 63.7% of patients were in stage IIIB, with a p-value of 0.107 (>0.05), suggesting no relationship between stage and response to neoadjuvant AC-T chemotherapy.

In terms of menstrual status, both postmenopausal and premenopausal groups exhibited a negative response of 7.1%, but premenopausal patients showed a higher positive response of 45.9%, with a p-value of 0.826 (>0.05), indicating no relationship between menstrual status and chemotherapy response. The most common histopathological type was invasive carcinoma non-specific (77.6%), with a p-value of 0.420 (>0.05), indicating no relationship between histopathological type and chemotherapy response. Lastly, grade III was the most prevalent (54.1%), with a p-value of 0.614 (>0.05), indicating no significant relationship between grade and chemotherapy response. The distribution of chemotherapy responses is presented in Table 2.

TABLE 2: Chemotherapy Response.

Chemotherapy Response	Sample (n=85)
Complete Response	12 (14.1%)
Partial Response	60 (70.6%)
Poor Response	2 (2.4%)
Stable Response	10 (11.8%)
Progressive Disease	1 (1.2%)

Note: 6MWT and VO2max are mean ± deviation; *p-value is significant when p<0.05.

Table 2 indicates that the most common chemotherapy response was partial response (70.6%), followed by complete response (14.1%) and stable response (11.8%).

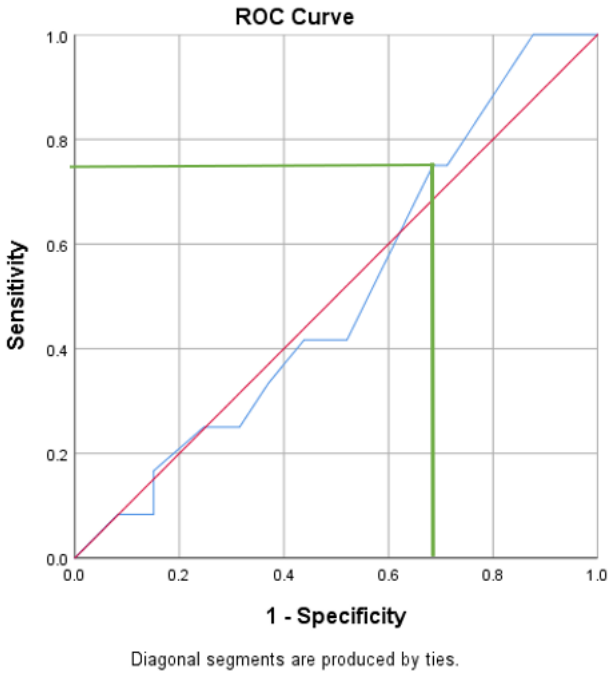

FIGURE 1: ROC Curve of Oestrogen Receptor Expression and Neoadjuvant AC-T Chemotherapy Response in TPBC Patients Post-MRM.

In this study, a ROC curve analysis was conducted to determine the threshold of oestrogen receptor expression concerning the response to neoadjuvant AC-T chemotherapy in TPBC patients post-MRM. The ROC graph results are displayed in Figure 1. The ROC analysis yielded an area under the curve (AUC) of 0.506 (95% CI: 0.343-0.669; p=0.950), with a sensitivity of 75.0% and specificity of 31.5%, indicating a threshold of oestrogen receptor expression at 17.5.

Bivariate analysis was performed using the Chi-Square test to assess the relationship between high oestrogen receptor expression (≥17.5) and the response to neoadjuvant AC-T chemotherapy in TPBC patients, along with the relative risk (RR). The results of the bivariate analysis are presented in Table 3, indicating that high ER levels in TPBC patients post-MRM were not significantly associated, with a p-value of 0.717.

TABLE 3: Relationship Between High Oestrogen Receptor Expression (≥17.5) and Neoadjuvant AC-T Chemotherapy Response in TPBC Patients Post-MRM Compared to Low Oestrogen Receptor Expression.

Variable	Neoadjuvant AC-T Response		RR	95% CI	p-value
	Negative Response (n=12)	Positive Response (n=73)			
ER% tinggi ≥17,5	9 (15,0%)	51 (85,0%)	1,250	0,369-4,236	0,717
ER% tinggi ≥17,5	3 (12,0%)	22 (88,0%)			

Note: *Chi-Square test significant at p<0.05.

A ROC curve analysis was conducted to determine the threshold of progesterone receptor expression concerning the response to neoadjuvant AC-T chemotherapy in TPBC patients post-MRM. The ROC graph results are displayed in Figure 2.

The ROC analysis yielded an AUC of 0.521 (95% CI: 0.360-0.682; p=0.815), with a sensitivity of 58.3% and specificity of 52.1%, indicating a threshold of progesterone receptor expression at 25.

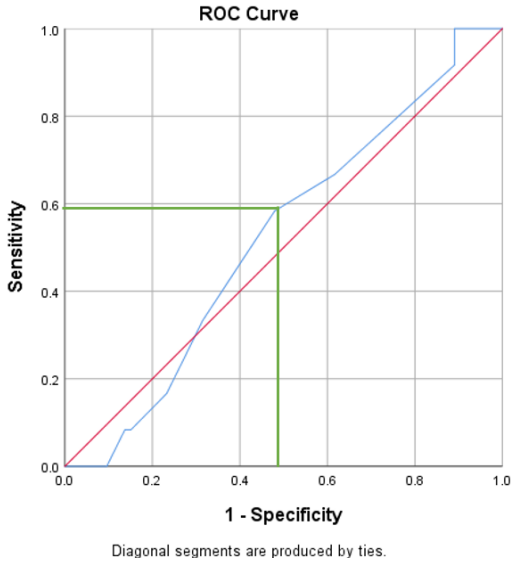

FIGURE 2: ROC Curve of Oestrogen Receptor Expression and Neoadjuvant AC-T Chemotherapy Response in TPBC Patients Post-MRM.

Bivariate analysis was performed using the Chi-Square test to assess the relationship between high progesterone receptor expression (≥25) and the response to neoadjuvant AC-T chemotherapy in TPBC patients, along with the relative risk (RR).

The results of the bivariate analysis are presented in Table 4, indicating that high PR levels in TPBC patients post-MRM were not significantly associated, with a p-value of 0.505.

TABLE 4: Relationship Between High Progesterone Receptor Expression (≥25) and Neoadjuvant AC-T Chemotherapy Response in TPBC Patients Post-MRM Compared to Low Progesterone Receptor Expression.

Variable	Neoadjuvant AC-T Response		RR	95% CI	p-value
	Negative Response (n=12)	Positive Response (n=73)			
High PR% (≥25)	7 (16,7%)	35 (83,3%)	1,433	0,494-4,162	0,505
Low PR% (<25)	5 (11,6%)	38 (88,4%)			

Note: *Chi-Square test significant at p<0.05.

In this study, an ROC curve analysis was conducted to determine the threshold of KI-67 expression concerning the response to neoadjuvant AC-T chemotherapy in TPBC patients post-MRM. The ROC graph results are displayed in Figure 3.

The ROC analysis yielded an AUC of 0.465 (95% CI: 0.251-0.679; p=0.700), with a sensitivity of 58.3% and specificity of 41.1%, indicating a threshold of KI-67 expression at 35.

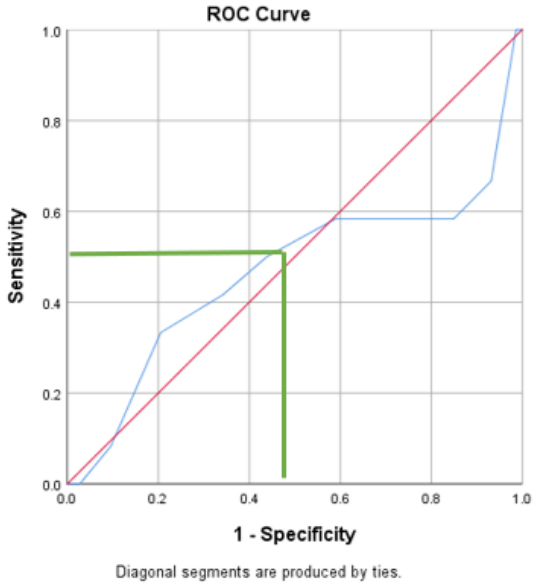

FIGURE 3: ROC Curve of Oestrogen Receptor Expression and Neoadjuvant AC-T Chemotherapy Response in TPBC Patients Post-MRM.

Bivariate analysis was performed using the Chi-Square test to assess the relationship between low KI-67 expression (≤35) and the response to neoadjuvant AC-T chemotherapy in TPBC patients, along with the relative risk (RR).

The results of the bivariate analysis are presented in Table 5.5, indicating that low KI-67 levels in TPBC patients post-MRM were not significantly associated, with a p-value of 0.970.

TABLE 5: Relationship Between Low KI-67 Expression (≤35) and Neoadjuvant AC-T Chemotherapy Response in TPBC Patients Post-MRM Compared to High KI-67 Expression.

Variable	Neoadjuvant AC-T Response		RR	95% CI	p-value
	Negative Response (n=12)	Positive Response (n=73)			
Low KI-67 (≤35)	5 (14,3%)	30 (85,7%)	1,020	0,352-2,955	0,970
High KI-67 (>35)	7 (14,0%)	43 (86,0%)			

Note: *Chi-Square test significant at p<0.05.

DISCUSSION

The study results indicated that the average age in the negative response group to neoadjuvant chemotherapy AC-T was 48.08 years, whereas the average age in the positive response group to neoadjuvant chemotherapy AC-T was 49.7 years. This aligns with the findings of Zeng et al. (2022), who reported the median age of patients with triple-negative breast cancer (TNBC) as 47 years [12]. Similarly, You et al. (2018), found that the age range of TNBC patients was predominantly between 40 and 49 years [7]. A study comparing the positive estrogen receptor group with the negative estrogen receptor group found average ages of 53.9 years and 52.4 years, respectively; however, no statistical correlation was found between age and estrogen receptor status [14]. Comparable studies reported a median age of TNBC patients as 47 years, with a range of 20 to 83 years [15].

The description of the age at menarche across all groups in this study was consistent, recorded at 13.5 years and 13.6 years. This is in agreement with the findings of Landmann et al. (2018), who reported an age range for menarche of 12.8 years to 13.1 years [14]. In this study, a greater number of patients were found to be in stage IIIB of cancer, accounting for 63.7%.

Menstrual status revealed that both postmenopausal and premenopausal patients exhibited a similar negative response rate of 7.1%, although premenopausal patients demonstrated a higher positive response rate of 45.9%. This contrasts with the findings of Landmann et al. (2018), who reported that postmenopausal patients had a response rate exceeding 50% [14]. Similar studies found that the majority of TNBC cases occurred in premenopausal women, accounting for 61.3%.[15] The predominant histopathological type identified was invasive carcinoma, not otherwise specified, at 77.6%. Different findings were reported regarding the proportion of tumours with triple-negative immunohistochemistry, which varied by histological type: medullary carcinoma (22.4%), adenoid cystic carcinoma (48.1%), and metaplastic carcinoma (53.0%) [16].

Cancer grading revealed that grade III was the most prevalent, at 54.3%. This finding is consistent with the study by Zeng et al. (2022), which also reported grade III as the most common grade (54.1%)[12]. In contrast, You et al. (2018) found that grade II was the most prevalent, at 50.3% [7]. While Razeq et al. (2021), reported that 54.7% of patients had grade III tumours at the time of diagnosis [15].

The study results indicated no association between high estrogen receptor levels and negative responses to neoadjuvant chemotherapy AC-T in patients with triple-positive breast cancer (TPBC). In this study, estrogen receptors were categorised using the Allred score, which combines the percentage of positive cells and the intensity of the reaction product in most carcinomas, with the combined score yielding a final score with eight possible values. The Allred score can be used to assess the effects of hormonal therapy administered [17]. The regimen and dosage of adjuvant chemotherapy did not provide preferential benefits for optimising the regimen and schedule of chemotherapy according to ER expression. ER-negative tumours derived greater benefits from neoadjuvant chemotherapy compared to ER-positive tumours. The findings revealed that ER-positive tumours exhibited a lower pathological response rate to neoadjuvant chemotherapy than ER-negative tumours. Furthermore, ER expression was found to be an independent predictor of pathological response in a nomogram developed for neoadjuvant chemotherapy [15].

Estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) have routinely been assessed in the management of breast cancer. This not only aids in prognosis but also assists in determining treatment options. The purpose of assessing receptor status is to provide appropriate treatment. The role of the pathologist is to accurately evaluate these biomarkers, while the oncologist's role is to treat patients with one of several prescribed therapies, depending on hormonal status. ER and PR are hormone receptors found in breast cells that receive hormonal signals that promote cell growth [17].

There are significant benefits from the use of chemotherapy among postmenopausal patients with HR-negative tumours, whereas postmenopausal patients with HR-positive tumours and premenopausal patients do not benefit from this treatment [18].

Breast cancer is termed ER-positive (ER+) if it possesses receptors for the hormone estrogen, which receives signals from estrogen and promotes growth, similar to normal cells. Likewise, breast cancer is termed PR-positive (PR+) if it has receptors for the hormone progesterone, allowing cancer cells to receive signals from progesterone that can enhance their growth. Similarly, HER2 status in breast carcinoma indicates that the HER2 gene produces excessive amounts of the HER2 protein. The HER2 protein is a receptor on breast cells that typically regulates the growth, division, and repair of healthy breast cells. However, in approximately 30% of breast cancers, the HER2 gene does not function correctly, leading to excessive production of its copies (known as HER2 gene amplification). These extra copies of the HER2 gene instruct breast cells to produce too many HER2 receptors (overexpression of HER2 protein), ultimately causing breast cells to grow and divide uncontrollably [17].

AC-T chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel), also referred to as AC-T or AC-Taxol, is a combination chemotherapy treatment used for breast cancer. Doxorubicin works by damaging the DNA within cancer cells, thereby halting their division, which leads to the death of cancer cell DNA. Cyclophosphamide attaches to and damages the DNA of cancer cells while they are in a resting phase (not dividing). Once the DNA of cancer cells is damaged, they can no longer continue to divide, and their growth slows or ceases. Paclitaxel works by damaging the structures that support cancer cells, preventing them from growing and dividing. Docetaxel (Taxotere) works similarly and is sometimes used as a substitute for paclitaxel [19].

The primary female sex hormone, estrogen, is responsible for regulating the functions of the female reproductive system, as well as the development of secondary sexual characteristics that emerge during puberty and sexual maturity. Estrogen exerts its effects by binding to estrogen receptors (ER), which in turn activate transcription processes and/or signalling events that control gene expression. These actions can be mediated by the direct binding of the estrogen receptor complex to specific sequences in gene promoters (genomic effects) or through mechanisms that do not involve direct binding to DNA (non-genomic effects) [20].

Neoadjuvant studies have tested the targeting of combined receptor blockade of both HER2 and ER. The demonstration of significant clinical benefits from combined receptor blockade strategies targeting HER2 and ER has been utilised in neoadjuvant settings, although this may be limited by the constraints of the number of therapeutic cycles administered in the preoperative setting. Additionally, such trials often use pathological complete response (pCR) as the primary clinical endpoint, whereas in the design of adjuvant trials (with a longer duration of combined receptor blockade in the postoperative setting), the primary clinical endpoint may be time-to-event (e.g., invasive disease-free survival) [21].

Patients with ER-positive breast cancer show benefits from endocrine therapy and have better survival rates compared to women with ER-negative tumours. Despite these benefits, up to 30% of patients subsequently develop recurrence or distant metastasis, possibly due to heterogeneity in the biological characteristics of ER-positive tumours. Therefore, it is clinically important to identify predictive and prognostic factors associated with outcomes in patients treated with tamoxifen [22]. HER2-negative breast cancer with low ER/PR expression (1–10%) has a gene expression profile similar to that of triple-negative breast cancer (TNBC)[23].

The study results indicated no association between high progesterone receptor levels and negative responses to neoadjuvant chemotherapy AC-T in patients with TPBC. Progesterone is a steroid hormone involved in the menstrual cycle, pregnancy, and embryogenesis, binding to progesterone receptors. Progesterone acts as a proliferative hormone in the breast, although paradoxically it inhibits the reproductive system and ovaries [24]. Progesterone serves as a risk factor in the early stages of breast tumorigenesis by stimulating the expansion of target breast cells undergoing transformation and promoting the development of early-stage lesions into invasive ductal cancer. Progesterone can induce in vitro migration of breast cancer cells, downregulating E-cadherin in breast tumours, which is a crucial step for epithelial-to-mesenchymal transition (EMT) and initiating luminal-to-my epithelial changes in subsets of tumour cells [25].

Epidemiological studies indicate that greater exposure to progesterone throughout a person's life leads to a higher likelihood of developing breast cancer. Similarly, synthetic progestins, whether administered in hormone replacement therapies (HRT) for postmenopausal management or as hormonal contraception in premenopausal women, confer an increased risk of breast cancer. Several epidemiological studies link progestin-containing contraceptives to an elevated risk of breast cancer [24]. Women who use progestin in conjunction with estrogen in hormone replacement therapies have a higher risk of developing breast tumours. The uncontrolled action of progesterone receptors in pre-neoplastic breast tissue contributes to the development of breast cancer [26].

In normal non-pregnant women's breasts, the frequency of ER/PR-positive luminal cells is relatively low. However, in human breast tissue, the frequency of proliferation of ER/PR-positive cells

progressively increases from 15-30% found in normal breast tissue, through ductal hyperplasia, atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS). The majority of breast cancers are ER/PR-positive at initial diagnosis. These data suggest that paracrine signalling pathways mediated by progesterone receptors are disrupted in pre-invasive lesions and cancer, with a shift towards autocrine regulation [27].

Tumour cells can express multiple types of steroid receptors that also cross-interact; progesterone and estrogen receptors are typically co-expressed, and it is becoming increasingly clear that their actions are interdependent on their expression and activity. Estrogen receptors have been shown to interact with progesterone receptors, and this complex is necessary for the rapid signalling induced by progestins and the transcriptional regulation of several progesterone receptor target genes. Anti-estrogens can prevent these effects by disrupting the ER/PR complex, although they do not block the binding of progesterone receptors to promoter regions [28].

This ER/PR transcriptional complex is confirmed by CHIP-seq analysis to bind to chromatin. Specifically, in breast cancer cells cultured in media containing estrogen, progestin treatment induces the binding of progesterone receptors to estrogen receptors, and the genomic binding of estrogen receptors is dominantly shifted from estrogen response elements (ERE) to progesterone response elements (ERP). This combined treatment can inhibit estrogen-induced growth in ER/PR-positive primary tumour xenograft models and explants, and negate estrogen-induced proliferation, migration, and invasion of cells. Collectively, these studies confirm that there is extensive cross-talk between progesterone and estrogen receptors, suggesting that they may act antagonistically or synergistically [29].

AC-T can be administered post-surgery as adjuvant therapy or pre-surgery as neoadjuvant therapy. Sometimes, the AC portion is given before surgery and the taxane afterwards, depending on cancer remaining in the breast after surgery. AC-T is typically administered in eight treatment cycles, every three weeks. The first four treatments consist of AC, followed by four treatments of paclitaxel (T). Paclitaxel can be given weekly at a lower dose than every three weeks. The entire AC-T treatment regimen lasts approximately five months [19].

Research indicating that low Ki-67 expression is not associated with negative responses to neoadjuvant chemotherapy AC-T in patients with triple-positive breast cancer (TPBC) can be explained by several factors. Firstly, although Ki-67 is often used as a marker of cell proliferation, its role as a predictor of chemotherapy response remains controversial. Some studies suggest that Ki-67 expression does not always correlate with clinical responses to neoadjuvant chemotherapy in locally advanced breast cancer.

Additionally, TPBC is characterised by positive expression of estrogen receptors (ER), progesterone receptors (PR), and HER2. The presence of these three receptors can complexly influence the response to therapy. For instance, positive HER2 expression is often associated with a good response to HER2-targeted therapies, regardless of Ki-67 expression levels. This indicates that factors other than Ki-67, such as hormonal receptor status and HER2, play significant roles in determining responses to chemotherapy.

Finally, variability in the assessment of Ki-67 expression through immunohistochemistry can affect the consistency of results. Differences in laboratory techniques and interpretations can lead to variations in Ki-67 expression assessments, thereby reducing its reliability as a single predictor of chemotherapy response. Therefore, it is essential to consider various biological and clinical factors comprehensively when evaluating therapeutic responses in TPBC patients [30].

This study is consistent with research by Liu et al. (2013), which found that Ki-67 has potential as a predictive factor for chemotherapy response in HR-positive breast cancer. HR-positive breast cancer patients with high Ki-67 levels are more sensitive to anthracycline/taxane chemotherapy regimens than those with low Ki-67 levels. A cut-off value of ≥19% is used to assess prognosis in HR-positive breast cancer patients receiving chemotherapy [5].

Ki-67 has also been used as a marker to determine molecular subtypes of breast cancer. One researcher combined Ki-67 with a panel of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER-2), finding that a Ki-67 level of 13% could distinguish luminal A cancers with a good prognosis from luminal B cancers with a more negative prognosis. Nine hundred and forty-three patients with node-negative breast cancer, who did not receive systemic therapy, were classified by subtype using these four immunohistochemical (IHC) markers: ER, PR, HER-2, and Ki-67, and were followed to observe recurrence and cancer-specific survival over ten years. Luminal B cancers with Ki-67 >14% had a significantly worse prognosis for recurrence and mortality compared to those with luminal A tumours with Ki-67 <14% (Soliman & Yussif, 2016). High Ki-67 levels are associated with good responses to neoadjuvant chemotherapy. Conversely, ER-positive cancers with low Ki-67 levels are better managed with 4–8 months of neoadjuvant hormonal therapy. However, the strength of initial Ki-67 values in predicting responses to specific adjuvant chemotherapy regimens has yet to be established [30].

CONCLUSIONS

The study found that the expression levels of ER, PR, and Ki-67 do not significantly correlate with the response to neoadjuvant AC-T chemotherapy in patients with TPBC.

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