Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Jun 05; 10(B):1440-1445.
https://doi.org/10.3889/oamjms.2022.9940
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Oncology*

Exploring the Expression of Survivin on Neoadjuvant Chemotherapy in Invasive Breast Carcinoma

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Edited by: Ksenija Bogoeva-Kostovska
Citation: Rustamadji P, Wiyarta E, Anggreani I. Exploring the Expression of Survivin on Neoadjuvant Chemotherapy in Invasive Breast Carcinoma. Open-Access Maced J Med Sci. 2022 Jun 05; 10(B):1440-1445. https://doi.org/10.3889/oamjms.2022.9940
Keywords: Survivin; Taxane; Chemotherapy; Breast Cancer; Invasive
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Received: 24-Apr-2022
Revised: 23-May-2022
Accepted: 26-May-2022

Funding: This research did not receive any financial support
Competing Interest: The authors have declared that no competing interest exists

Abstract

BACKGROUND: Biomarkers are required to monitor the response to neoadjuvant chemotherapy (NC) in patients with invasive breast cancer (IBC).

AIM: The purpose of this study is to determine the function of survivin in the administration of NC, both taxane and non-taxane based, to patients with IBC.

METHODS: Thirty-one samples were categorized according to the NCs administrative status (before or after) and the type of NC used (taxane or non-taxane based). Age, tumor grade, receptor status (ER, PR, HER2, and Ki-67), and survivin expression were evaluated. Survivin expressions were evaluated by IHC staining and categorized according median H-score cutoffs, while other data were collected from archives. Data were gathered and analyzed using generalized linear model.

RESULTS: Survivin expression decreased following NC administration, although not significantly ($p = 0.285$). The taxane group had lower survivin expression. Statistically, this was not significant ($p = 0.329$). The non-taxane group had the same outcome ($p = 0.792$). The decline in survivin expression was greater in the taxane group than in the non-taxane group, although it was not statistically significant ($p = 0.369$).

CONCLUSION: Although the changes in survivin expression were not statistically significant, when clinical and laboratory data are analyzed, survivin expression has the potential to be a predictive biomarker of NC response as well as clinical outcome in IBC.

Introduction

Breast cancer is the most common type of cancer in women and the primary cause of death from cancer. Female breast cancer is the most often diagnosed in 2020, accounting for 11.7% of overall cases and 6.9% of cases associated with death, according to Global Burden Cancer (GLOBOCAN) data for both sexes combined [1]. Breast cancer is a malignant tumor of the breast tissue characterized as either invasive or non-invasive. Invasive breast carcinoma (IBC) is a more common kind of breast cancer classified into numerous subgroups [2], [3], [4].

Chemotherapy is a critical component of contemporary IBC care, particularly chemotherapy administered before surgery, referred to as neoadjuvant chemotherapy (NC) [5]. NC is currently the gold standard for locally growing breast cancer and a more often employed therapeutic option for people with an operable disease in its early stages [5]. NC is classified into two broad categories: Taxane based and non-taxane based [6]. Taxane is one of the most successful and widely used systemic treatments in breast cancer treatment [6]. However, the resistance to NC affects breast cancer care.

Cancer cells have developed a strategy of self-protection to counteract the effects of NC through the activation of intracellular pathways [7]. NFkB activation is one well-known pathway [7]. NFkB is a multiprotein complex that has a variety of roles in the cell, most notably in gene regulation. NFkB's capacity to generate resistance to chemotherapy is mediated by its regulatory involvement in various anti-apoptotic genes [7]. These genes include pro-survival genes such as cyclin D1; anti-apoptotic genes such as survivin; and pro-survival genes such as x-IAP [7], [8], [9]. Survivin contributes significantly to cell apoptosis inhibitory signals through this pathway [10]. Due to survivin's role in the NC resistance pathway, it has the potential to be used as a predictive biomarker. Predictive biomarkers signal a patient's responsiveness or resistance to a certain NC therapy [11]. Thus, the ultimate therapeutic objective of predictive biomarkers is to enhance overall survival following treatment of certain NC. This study explores the survivin expression in IBC before and after NC for both taxane based and non-taxane based. We hypothesized that survivin expression has a relationship with NC administration in patients with IBC.

Materials and Methods

Study design and data collection

From November 2021 to April 2022, this retrospective cohort research was undertaken at the Faculty of Medicine, University of Indonesia, Anatomical Pathology Laboratory. In November 2021, the Faculty of Medicine at the University of Indonesia's Ethics Committee accepted the Faculty's experimental protocols under protocol number 21-11-1252. Each individual provided written consent and understood the study's purpose. The study conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki) [12]. All data were extracted from departmental archives between January 2014 and June 2016, with a 5-year observation period beginning in January 2019 and ending in June 2021. Patient age, tumor grade, tumor size, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, Ki67 status, axillary lymph node metastasis (ALNM), lymphovascular invasion (LVI), and NC type (taxane based or non-taxane based) were all collected. In addition, data on survivin expression were collected by quantifying the findings of IHC staining on the paraffin block.

Samples

This analysis employed primary tumor paraffin blocks from female breast mastectomy patients who were histopathologically diagnosed with IBC for the 1st time. We exclude samples from patients with a histopathological condition other than IBC, those with systemic comorbidities (diabetes and hypertension), and those with dubious paraffin blocks (e.g., broken or weakened paraffin blocks). The samples were categorized according to the NCs administrative status (before or after) and the type of NC used (taxane or non-taxane based). The sample selected represents the largest possible total sample from the department archives. Only one researcher had access to the grouping findings (E.W.) to minimize bias. Other researchers were blinded to the classifications into which each study falls until the analysis was complete.

Slide preparation and IHC staining

The staining technique is followed by Primariadewi *et al*. (2021) and Kusmardi *et al*. (2021) [3], [4], [13], [14]. According to standard protocols, a paraffin slice of a breast cancer specimen was deparaffinized in xylol (Merck, Jakarta, Indonesia) and rehydrated for 5 min in a 96%, 70%, and distilled water series (Merck, Jakarta, Indonesia). Heat-induced antigen retrieval was performed for 20 min in Tris-EDTA (Brataco Inc., Jakarta, Indonesia) at pH 9.0 in a 96°C Decloaking Chamber. After antigen retrieval, sections were treated with peroxidase block for 15 minutes before rinsing with phosphate-buffered saline (PBS) pH 7.4 for 15 minutes. Anti-survivin antibodies (ab469, Abcam, Cambridge, UK) were incubated on the slide for 1 hour followed by post-primary and Novolink polymer incubation. The chromogen for the brown color was diaminobenzidine (Abcam, Jakarta, Indonesia), and tissue slices were counterstained with hematoxylin (Abcam, Jakarta, Indonesia) and 5% lithium carbonate (Merck, Jakarta, Indonesia) before being viewed under a microscope.

Quantification of survivin expression

Two experts in reading histopathology slides (P.R. and I.A.) analyzed and evaluated the IHC staining. Each preparation was inspected under a light microscope at a total magnification of ×400 and documented using a computer running Leica LAZ EZ software and a camera equipped with a white balance setting in conjunction with a Leica DM750 microscope. Survivin expression was determined in at least 500 tumor cells randomly picked from five independent visual fields (×400). A minimum of 100 tumor cells represented each location. The presence of survivin expression was revealed by brown staining of the tumor cell membrane and cytoplasm [15], [16]. Based on the strength of the brown color measured in each field of view using QuPath cell counter, staining intensity was classified as no staining (0), low positive (1+), positive (2+), and high positive (3+) [17]. The H-score is used to measure the expression of survivin. The H-score is computed using the following formula: H-score = (percentage of low positives × 1) + (percentage of positives × 2) + (percentage of high positive × 3) [18]. Two observers independently computed the H-scores for the whole sample (P.R. and I.A.). To reduce bias, the results of previously investigated calculations are compiled and given to further researchers (E.W.) until the entire sample is assessed. The mean H-score of the two observers will be used in further analyses.

Statistical analysis

Before analysis, data collection was entered into a primary table using Microsoft Excel (Microsoft Corp, Redmond, WA, USA). The tabulated data were analyzed and visualized using the Statistical Package for the Social Sciences/SPSS version 20 (IBM Corp., Armonk, NY, USA). The median H-score is the cutoff (median split approach) to classify the survivin expression [3]. According to the H-score cutoff, the two observers' H-scores were averaged and classified as high or low. These categories denote the level of survivin expression in each sample.

Results

All 31 underwent IHC staining for survivin expression. Each sample has clinicopathologic characteristics, as shown in Tables 1 and 2 before and after NC administration. The results of representative IHC staining are shown in Figure 1. Each image provides a sample of tumor cells with different staining groups, including negative, low positive, positive, and high positive. The images represent a collection of visual fields taken from the same slide. The intensity of the brown color in these slides is measured and converted into an H-score for future investigation. Two observers (P.R. and I.A.) assessed all 31 samples independently.

Table 1: Clinicopathological characteristic before neoadjuvant chemotherapy administration

Variables	Category	Survivin expression		p-value
		High (%)	Low (%)	
Age	≥50 y.o.	8 (50.0)	8 (50.0)	0.567
	<50 y.o.	9 (60.0)	6 (40.0)	
Tumor grade	3	6 (66.7)	3 (33.3)	0.575
	2	10 (52.6)	9 (47.4)	
	1	1 (33.3)	2 (66.7)	
ER status	Positive	9 (60.0)	6 (40.0)	0.576
	Negative	8 (50.0)	8 (50.0)	
PR status	Positive	6 (42.9)	8 (57.1)	0.224
	Negative	11 (64.7)	6 (35.3)	
HER2 status	Positive	8 (57.1)	6 (42.9)	0.815
	Negative	9 (52.9)	8 (47.1)	
Ki67 status	Positive	4 (80.0)	1 (20.0)	0.217
	Negative	13 (50.0)	13 (50.0)	
Taxane	With	7 (70.0)	3 (30.0)	0.242
	Without	10 (47.6)	11 (52.4)	

ER: Estrogen receptor; PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2. Univariate analysis was performed using the Chi-square test with continuity correlation. *p < 0.05 is considered statistically significant.

As indicated in Table 3 and Figure 2, the change in survivin expression between before and after NC administration was overall lowering but not statistically significant (p = 0.285). The samples were then divided into two groups according to the kind of NC received, taxane and non-taxane based, as shown in Table 4 and Figure 3.

Survivin expression decreased in the taxane-based group. However, this was not statistically significant (p = 0.329). The identical result was seen in the non-taxane-containing group (p = 0.792). The difference in survivin expression between the two

Table 2: Clinicopathological characteristic after neoadjuvant chemotherapy administration

Variables	Category	Survivin expression		p-value
		High (%)	Low (%)	
Age	≥50 y.o.	7 (43.8)	9 (56.3)	0.870
	<50 y.o.	7 (46.7)	8 (53.3)	
Tumor grade	3	3 (27.3)	8 (72.7)	0.246
	2	9 (60.0)	6 (40.0)	
	1	2 (40.0)	3 (60.0)	
ER status	Positive	8 (53.3)	7 (46.7)	0.376
	Negative	6 (37.5)	10 (62.5)	
PR status	Positive	6 (42.9)	8 (57.1)	0.815
	Negative	8 (47.1)	9 (52.9)	
HER2 status	Positive	6 (42.9)	8 (57.1)	0.815
	Negative	8 (47.1)	9 (52.9)	
Ki67 status	Positive	2 (40.0)	3 (60.0)	0.800
	Negative	12 (46.2)	14 (53.8)	
ALNM	Yes	8 (53.3)	7 (46.7)	0.376
	No	6 (37.5)	10 (62.5)	
LVI	Yes	6 (37.5)	10 (62.5)	0.376
	No	8 (53.3)	7 (46.7)	
Taxane	With	4 (40.0)	6 (60.0)	0.690
	Without	10 (47.6)	11 (52.4)	

ALNM: Axillary lymph node metastasis; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; LVI: Lymphovascular invasion, PR: Progesterone receptor. Univariate analysis was performed using the Chi-square test with continuity correlation. *p < 0.05 is considered statistically significant.

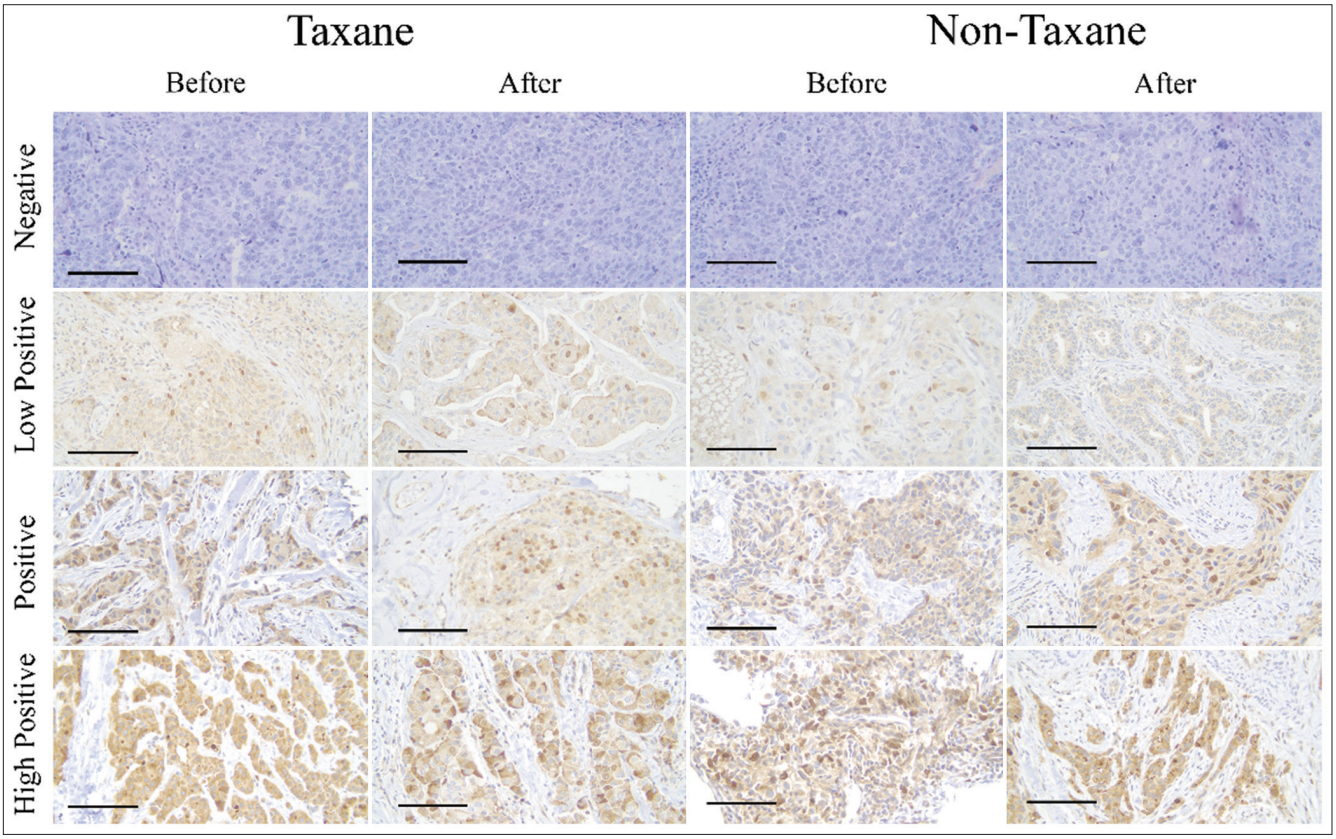

Figure 1: IHC staining for survivin expression in IBC tumor cells at ×400 before and after NC administration. Scale bar represents 50 μm for all images

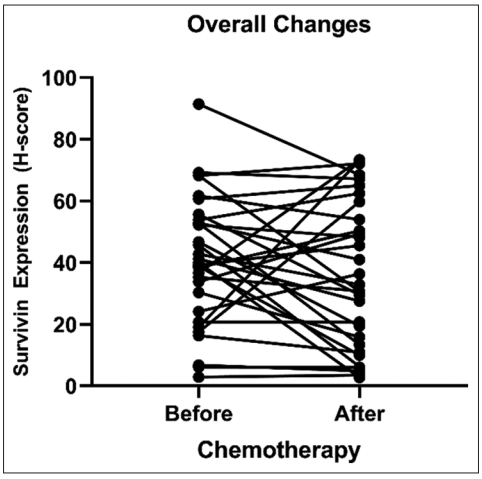

Figure 2: Individual before-after line showing overall changes in survivin expression before and after administration of neoadjuvant chemotherapy

groups was also analyzed. It was discovered that the drop in survivin expression was larger in the taxane-based group than in the non-taxane-based group.

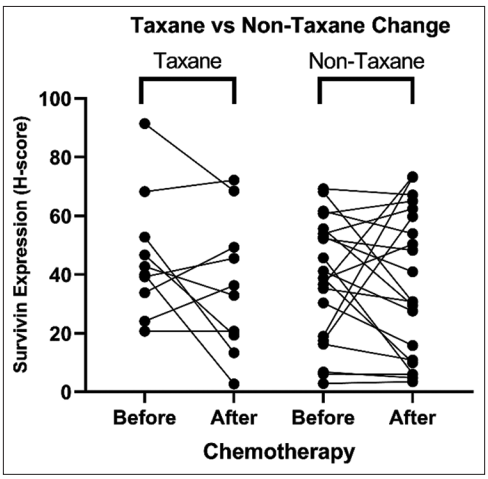

Figure 3: Individual before-after line showing changes in survivin expression before and after administration of neoadjuvant chemotherapy in taxane-based versus non-taxane-based group

Table 3: Overall changes in survivin expression before and after administration of neoadjuvant

Category	n	Survivin expression	p value
Before.	31	40.96 ± 20.74	0.285
After	31	36.50 ± 23.81	

Statistical analysis was performed using the independent t-test.

However, the difference was not statistically significant (p = 0.369).

Table 4: Changes in survivin expression before and after administration of neoadjuvant in taxane versus non-taxane group

Group	Category	n	Survivin expression	p value	Survivin expression mean difference	p value
Taxane	Before	10	45.99 ± 20.99	0.329	9.89 ± 23.86	0.369
	After	10	36.10 ± 23.02			
Non-taxane	Before	21	38.56 ± 20.69	0.792	1.87 ± 20.49	
	After	21	36.69 ± 24.74			

Statistical analysis was performed using the independent t-test and generalized linear model.

Discussion

Survivin expression changed significantly in IBC patients treated with NC. These changes can be detected on an individual level and in groups. In general, survivin expression decreased between pre-and post-NC administration. This indicates a relationship between the reduction in survivin in IBC cells in response to NC and a mechanism. This phenomenon can be explained by the fact that survivin is required for drug resistance and that modulating survivin expression impacts treatment efficacy. Therefore, several types of NC were designed to target this biomarker [19]. Numerous studies have established that certain cancer prevention medications work by decreasing survivin production [20] and that survivin overexpression is associated with chemoresistance to a variety of treatments, including adriamycin, cisplatin, and Taxol [21], [22], [23]. This also explains the difference in survivin expression between taxane- and non-taxane-treated NC.

Conclusion

In addition, the results of this study indicated that the taxane-based NC group had a higher drop in survivin expression than the non-taxane-based NC group. Numerous researches corroborate this conclusion. Wu *et al*. demonstrated that advanced non-small-cell lung cancer patients receiving taxane-platinum treatment had decreased survivin expression [24]. In addition, they demonstrated that increased tumor N-survivin expression is an independent predictor of clinical response to treatment (OR 6.14, 95% confidence interval [CI] 1.62–23.29; p = 0.008) [24]. According to Han *et al*., silencing survivin inhibits docetaxel-induced apoptosis in HeLa cells by increasing mitotic slippage [25]. They hypothesize that inhibiting survivin may affect the cell response to docetaxel by causing abnormal mitotic progression rather than immediately sensitizing cells to apoptosis [25]. The above studies also imply the potential of survivin as a biomarker predictor of NC in IBC, as also reported by Goricar *et al*. in malignant mesothelioma patients [26].

The outcomes of this research indicate that the use of survivin as a target in IBC treatment is gaining traction. One of these is in survivin's position as a target in immunotherapies, such as CDK4/6 inhibitors. Inhibiting CDK 4/6 generates a pro-apoptotic transcriptional program by suppressing survivin expression, while concurrently increasing caspase 3 expression in a retinoblastoma tumor suppressor-dependent way [27]. Numerous preclinical studies demonstrate the synergistic effect of CDK4/6 inhibitors

plus chemotherapy [28]. In addition, a CDK4/6 inhibitor in conjunction with chemotherapy is being evaluated in clinical studies to improve antitumor activity while minimizing toxicity [28]. Exploiting the CDK4/6 inhibitor's non-canonical effects may potentially give an impetus for future investigations in conjunction with chemotherapy [28].

Even though the research sample was drawn from an IBC referral center hospital, the sample size was still insufficient. One explanation for this constraint is that NC is not yet widely implemented at the study location. This led to a non-significant alteration in surviving expression. However, clinical and laboratory significance must be considered since both reveal a declining trend in surviving expression across all groups. In addition, this is an exploratory study to perform additional research on the role of survivin in IBC delivered through NC.

Although the changes in survivin expression were not statistically significant, when clinical and laboratory data are analyzed, survivin expression can be a predictive biomarker of NC response and clinical outcome in IBC. Additional research with bigger sample numbers and in-depth analysis is required to elucidate the involvement of survivin in NC in IBC.

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