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ORIGINAL ARTICLE

KIF15 expression characteristics: Relevance toneo-adjuvant chemotherapy efficacy in breast cancer*

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Abstract

Objective The relationship between the expression of kinesin family member 15 (KIF15) and clinicopathological features in breast cancer (BC) remains controversial. In this study, we aimed to explore the influence of KIF15 expression on the efficacy of neoadjuvant chemotherapy (NAC) and evaluate its clinical value in predicting prognosis for BC patients.

Methods Immunohistochemistry was used to detect KIF15 expression in 93 BC patients undergoing NAC to analyze the relationship between KIF15 expression and clinical efficacy and analytical parameters.

Results Of the 93 BC patients enrolled, 24.73% who underwent NAC had higher KIF15 expression levels, showing positive correlations with ER, HER-2, Ki67, and lymph node metastasis ($P < 0.05$). The clinical benefit of NAC was 70.97%, and the major histological response (MHR) rate was 61.29%. The effective therapeutic rate in patients with high KIF15 expression was 95.65%, while the MHR rate was 65.22%. Various molecular BC subtypes with varied clinical and pathological responses exhibited correlation to a large extent. Of all the BC patients studied, 84% of the triple-negative breast cancer (TNBC) patients were evaluated as clinically effective, and 52% of the TNBC patients were evaluated as pathologically effective, and these values were significantly higher than those of the other molecular types ($P < 0.05$). The expression of KIF15 in 25 TNBC patients showed positive correlations with lymph node metastasis.

Conclusion Overexpression of KIF15 was shown to increase BC sensitivity to chemotherapy and demonstrated better outcomes.

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Key words: breast cancer; neoadjuvant chemotherapy; KIF15; molecular subtypes

Breast cancer (BC) is the leading malignancy that seriously threatens the health of women [1–3]. Approximately 35% of the therapy failures in BC patients are attributed to tumor chemoresistance [4]. At present, there are no predictive biomarkers identified for assessing the therapeutic effects of adjuvant chemotherapy in BC patients. There is a certain degree of uncertainty in choosing chemotherapy regimens, and thus, we sought to identify an effective marker that might be a potential therapeutic target in BC and predict responses to chemotherapy.

Kinesin family member 15 (KIF15) belongs to the kinesin superfamily of proteins. Previous studies have reported that the overexpression of KIFC3, KIF5A, and KIF12 plays a role in mediating resistance to the chemotherapeutic agent docetaxel [5]. In BC, KIF15 is associated with poor prognosis [6–7], and therefore, KIF15 is expected to be a new marker of chemosensitivity and a target with therapeutic potential. Patients with locally advanced BC generally receive neoadjuvant

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chemotherapy (NAC) to shrink breast tumors prior to surgical removal. Another important role of NAC is in the evaluation of the effects of NAC regimens for guiding the selection of postoperative chemotherapy approaches [8–9]. Hence, in this study, the expression levels of KIF15 in tumor tissues of 93 BC patients were analyzed, and relationships involving KIF15 and clinicopathological parameters as well as NAC efficacy were evaluated.

Materials and methods

Patient cohort

Ninety-three primary invasive breast carcinoma specimens were obtained from the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (Shanghai, China) between 2016 and 2018. The inclusion criteria were as follows: (1) all patients with histopathological diagnosis of invasive BC; (2) all BC patients for whom immunohistochemical staining of KIF15 was performed for their tumors; (3) all patients who were at stage II or III according to the American Joint Committee on Cancer (AJCC) TNM staging system for BC (7th edition); and (4) patients with an Eastern Cooperative Oncology Group performance status of 0 or 2. The exclusion criteria were as follows: (1) patients with incomplete clinical data; (2) with distant metastasis; (3) who underwent NAC previously, and who received any anti-tumor therapy; and (4) with severe abnormality of liver and kidney function before undergoing NAC.

A total of 93 patients with a median age of 56 years (ranging between 28 and 75 years) were included. All women enrolled had single unilateral invasive BC lesions. All patients had primary lesions and none had undergone chemotherapy, radiotherapy, or endocrine therapy before surgical intervention. Estrogen receptor (ER), progesterone receptor (PR), HER2, and KI67 status was determined by immunostaining core-needle biopsy samples of BC tissues obtained before the initiation of NAC. Among the 93 patients, 92 had invasive ductal cancer (98.9%) and 1 patient (1.08%) had invasive apocrine adenocarcinoma. Molecular typing revealed 26 luminal A (28.0%), 21 luminal B (22.6%), 25 triple negative (26.9%) and 21 HER2-positive (22.6%) cases. Clinical staging before NAC showed that 49 patients were at stage II (52.7%) and 47 were at stage III (50.5%). This study was approved by the Institutional Review Board of the Yueyang Hospital of Integrated Chinese and Western Medicine affiliated with the Shanghai University of Traditional Chinese Medicine. All patients provided signed informed consent.

For all patients, paclitaxel (80 mg/m^2) was administered weekly starting from day 1 for 16 weeks, and cisplatin 25 mg/m^2 was given weekly on days 1, 8, and 15 every 28 days for four cycles as an NAC therapy regimen. HER2 positive patients could have trastuzumab concurrently with the chemo therapy in the neoadjuvant setting. The trastuzumab was given every week at 4 mg/kg (cycle 1), followed by 2 mg/kg, and used for a year. Postoperative chemotherapy for non-pCR patients was left to the discretion of the attending physician. Planned surgery was sequentially provided after neoadjuvant therapy. All procedures performed in this study involving human participants were done in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Immunohistochemistry (IHC)

ER, PR, Ki-67, HER2, and KIF15 levels were evaluated using paraffin-embedded tumor samples obtained via biopsy. ER, PR, HER2, and Ki-67 were detected using rabbit monoclonal antibodies SP1, EE2, 4B5 (Hoffmann-La Roche Ltd., Switzerland), and MIBI (Leica Biosystems Newcastle Ltd., UK). KIF15 was detected using a goat anti-KIF15 monoclonal antibody (Abcam, USA).

IHC staining results were judged by two independent pathologists from the Department of Pathology of our hospital. Positive ER and PR were defined as > 1% positive nuclear staining, and Ki-67 levels were recorded as a continuous value. HER2 assessments were conducted according to the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) recommendations, 2013 [10]. KIF15 evaluation was performed according to the following criteria. The percentage of positively-stained tumor cells was graded based on a four-point scale, which was as follows: (1) percentage of positive cells ≤ 10%; (2) 11% < percentage of positive cells ≤ 50%; (3) 51% < percentage of positive cells ≤ 75%; and (4) 76% < percentage of positive cells. IHC intensity scores were graded as follows: 0, no staining; 1, weak staining: light yellow; 2, moderate staining: yellow brown; and 3, strong staining: brown. According to the above two indicators, the results were divided into four levels: 0–3 (–), 4–5 (+), 6–7 (++), and ≥ 8 (+++). A score of 0–7 indicated low expression (–), and scores of ≥ 8 indicated high expression (+).

Efficacy evaluation

Efficacy evaluations included clinical and histopathological evaluations of BC lesions. Tumor assessment was performed every two months by physical examination, mammary magnetic resonance imaging (MRI), and ultrasonography. Clinical efficacy was ranked according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines [11]. Clinical efficacy evaluation was performed according to the World Health Organization (WHO) tumor lesion classification and

curative effect evaluation, including complete remission (CR), partial response (PR), no change (SD), and progress (PD). Effective chemotherapy refers to patients with CR or PR, and ineffective chemotherapy refers to patients with SD or PD.

Final pathological responses were assessed using the Miller-Payne grading system [11], in which pathological responses are divided into five grades based on tumor cellularity comparisons involving pre-NAC core biopsies and postoperative surgical specimens. Miller-Payne response grade 3 to 5 was considered as good pathological responses (GPRs), while grades 1 and 2 were considered as poor pathological responses (PPRs).

Statistical analysis

SPSS v.22.0 software was used for statistical analysis. Chi-square analysis, Fisher's exact probability test, and Spearman correlation coefficient analysis methods were used for investigation of KIF15 expression, clinicopathological parameters, and differences between subtypes. Statistical tests were two-sided with a significance level of $P < 0.05$.

Results

KIF15 expression and clinicopathological features

Expression of KIF15 in BC tumor tissues of patients who underwent NAC was detected by IHC (200 ×) (Fig. 1). The results showed that the expression of KIF15 was upregulated in 23 patients (23/93, 24.73%). Potential correlation between KIF15 expression and clinicopathological characteristics in BC patients was then analyzed. KIF15 exhibited positive correlations with ER ($P = 0.028$, $r = 0.228$), HER-2 ($P = 0.042$, $r = 0.211$), and KI67 expression ($P = 0.040$, $r = 0.213$). Furthermore, lymph node involvement ($P = 0.031$, $r = 0.224$) acted as a predictive factor of KIF15 expression. However, there was no significant correlation with age ($P = 0.980$, $r = 0.037$) or tumor size ($P = 0.862$, $r = 0.018$; Table 1).

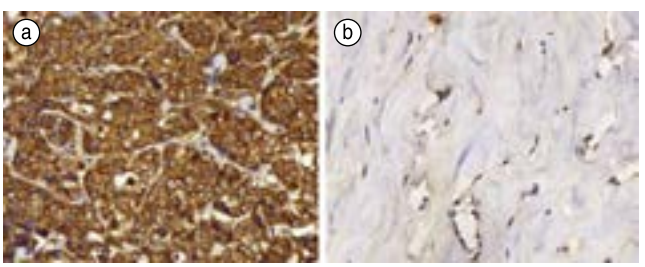

Fig. 1 Different expressions of KIF15 immunochemistry staining. (a) High expression; (b) Low expression

KIF15 expression and the clinical efficacy of NAC

Of the 93 patients, eight showed CR (8.60%), 58 showed PR (62.37%), 23 showed SD (24.73%), and four showed PD (4.30%). The total effective rate (CR + PR) was 70.97% (66/93). The effective chemotherapy rate of NAC in patients with high KIF15 expression was 95.65% (22/23), whereas the effective chemotherapy rate in BC patients with negative or low KIF15 expression was 62.86% (44/70), showing statistically significant differences ($P = 0.003$, $r = 0.312$). Furthermore, HER2 gene amplification ($P = 0.047$, $r = 0.206$) and high Ki-67 proliferation ($P = 0.048$, $r = 0.205$) were also found to be predictive factors of clinical efficacy in NAC therapy (Table 2).

KIF15 expression and histopathological evaluation of NAC

Of the 93 patients, six had MP1 (6.45%), 51 had MP2 (54.84%), 20 had MP3 (21.51%), 5 had MP4 (5.38%), and 11 had MP5 (11.83%). The GPR (MP3~5) was 61.29% (36/93), and the GPR rate in the high KIF15 expression NAC group was 65.22% (15/23). The GPR rate in the high KIF15 expression group was significantly higher than that in the low KIF15 expression group, and the difference was statistically significant ($P = 0.003$, $r = 0.312$). Furthermore, HER2 amplification ($P = 0.006$, $r = 0.285$) also acted as a predictive factor for histopathological evaluation of NAC (Table 3).

Table 1 Correlation between KIF15 expression and clinicopathological features of patients with BC receiving neoadjuvant chemotherapy [*n* (%)]

Variables	*n*	Age (years)		Lymph node involvement		Tumor size (cm)		ER		HER2		Ki-67	
		> 40	≤ 40	> 0	= 0	> 5	≤ 5	Positive	Negative	Positive	Negative	>14%	≤14%
High expression	23	19 (82.61)	4 (17.39)	21 (91.30)	2 (8.70)	6 (26.09)	17 (73.91)	19 (82.61)	4 (17.39)	18 (78.26)	5 (21.74)	20 (86.96)	3 (13.04)
Low expression	70	60 (85.71)	8 (14.29)	46 (68.57)	22 (31.43)	17 (24.29)	53 (75.71)	40 (57.14)	30 (42.86)	38 (54.29)	32 (45.71)	45 (64.29)	25 (35.71)
X^2		0.001		4.673		0.030		4.841		4.154		4.228	
P		0.980		0.031		0.862		0.028		0.042		0.040	
r		0.037		0.224		0.018		0.228		0.211		0.213	

Table 2 Correlation between KIF15 expression and the clinical efficacy of neoadjuvant chemotherapy in BC [*n* (%)]

Variables	*n*	Clinical effectiveness						X^2	*P*	*r*
		CR	PR	SD	PD	Effective	Ineffective			
ER										
Positive	41	2 (4.88)	24 (58.54)	11 (26.83)	4 (9.76)	26 (63.41)	15 (36.59)	2.030	0.154	–0.148
Negative	52	6 (11.54)	34 (65.38)	12 (23.08)	0 (0.00)	40 (76.92)	12 (23.08)			
HER2										
Positive	56	6 (10.71)	38 (67.86)	11 (19.64)	1 (1.79)	44 (78.57)	12 (21.43)	3.950	0.047	0.206
Negative	37	2 (5.41)	20 (54.05)	12 (32.43)	3 (8.11)	22 (59.46)	15 (40.54)			
Ki-67										
>14%	74	8 (10.81)	48 (64.86)	16 (21.62)	2 (2.70)	56 (75.68)	18 (24.32)	3.897	0.048	0.205
≤14%	19	0 (0.00)	10 (52.63)	7 (36.84)	2 (10.53)	10 (52.63)	9 (47.37)			
KIF15										
High expression	23	5 (21.74)	17 (73.91)	0 (0.00)	1 (4.35)	22 (95.65)	1 (4.35)	9.037	0.003	0.312
Low expression	70	3 (4.29)	41 (58.57)	23 (32.86)	3 (4.29)	44 (62.86)	26 (37.14)			
All	93	8 (8.60)	58 (62.37)	23 (24.73)	4 (4.30)	66 (70.97)	27 (29.03)			

Table 3 Correlation between KIF15 expression and histopathological evaluation of neoadjuvant chemotherapy in BC [*n* (%)]

Variables	*n*	Histopathological evaluation							X^2	*P*	*r*
		MP1	MP2	MP3	MP4	MP5	GPR	PPR			
ER											
Positive	43	2 (4.65)	23 (53.49)	5 (11.63)	5 (11.63)	8 (18.60)	18 (41.86)	25 (58.14)	0.335	0.563	0.060
Negative	50	4 (8.00)	28 (56)	15 (30.00)	0 (0.00)	3 (6.00)	18 (36.00)	32 (64.00)			
HER2											
Positive	56	2 (3.57)	26 (46.43)	19 (33.93)	3 (5.36)	6 (10.71)	28 (50.00)	28 (50.00)	7.563	0.006	0.285
Negative	37	4 (10.81)	25 (67.57)	1 (2.70)	2 (5.41)	5 (13.51)	8 (21.62)	29 (78.38)			
Ki-67											
>14%	74	5 (6.76)	42 (56.76)	16 (21.62)	3 (5.36)	8 (10.81)	27 (36.49)	47 (63.51)	0.755	0.385	0.090
≤14%	19	1 (5.26)	9 (47.37)	4 (21.05)	2 (5.41)	3 (15.79)	9 (47.37)	10 (52.63)			
KIF15											
High expression	23	2 (8.70)	6 (26.09)	7 (30.43)	2 (4.05)	6 (26.09)	15 (65.22)	8 (34.78)	9.050	0.003	0.312
Low expression	70	4 (5.71)	45 (64.29)	13 (18.57)	3 (10.53)	5 (7.14)	21 (30.00)	49 (70.00)			
All	93	6 (6.45)	51 (54.84)	20 (21.51)	5 (5.38)	11 (11.83)	36 (38.71)	57 (61.29)			

Molecular subtypes of BC and efficacy of NAC

No significant differences were observed in terms of age, tumor size, and lymph node metastasis in four different subtypes of BC among patients. Correlations between molecular subtypes and clinical efficacy of NAC in BC ($P = 0.035$, $r = 0.358$). The effective rate (CR + PR) in TNBC patients was 84% (21/25), which was higher than that of the other three molecular subtypes. Histopathological evaluations also showed similar results, in which the GPR rate remained the highest in TNBC patients (52%, 13/25). In addition, KIF15 expression levels exhibited associations with the four different subtypes of BC. Elevated expression of KIF15 was detected in 44% (11/25) of the TNBC patients. Compared with the other three types of molecular typing, the difference was statistically significant ($P = 0.031$, $r = 0.148$) (Table 4).

KIF15 expression and NAC efficacy in TNBC patients

Results for 25 TNBC patients from the 93 patients who underwent NAC were analyzed. KIF15 was positively correlated with lymph node involvement ($P = 0.042$, $r = 0.435$) and histopathological evaluation ($P = 0.015$, $r = 0.529$) (Table 5). In the high KIF15 expression group, 10 patients (90.91%) had lymph node metastases, and this number was higher than that of the low KIF15 expression group. In addition, the GPR rate in the high KIF15 expression group (81.82%, 9/11) was higher than that in the low KIF15 expression group (28.57%, 4/13). However, there was no significant correlation with clinical effectiveness ($P = 0.105$, $r = 0.387$) and tumor size ($P = 0.056$, $r = 0.445$; Table 5).

Table 4 Correlation between the molecular subtypes of BC and the efficacy of neoadjuvant chemotherapy [*n* (%)]

Variables	*n*	Age		Lymph node involvement		Tumor size		Clinical effective		Histopathological evaluation		KIF15 expression	
		> 40	≤ 40	> 0	= 0	> 5 cm	≤ 5 cm	Effective	Ineffective	GPR	PPR	High	Low
Luminal A	26	20 (76.92)	6 (23.08)	21 (80.77)	5 (19.23)	6 (23.08)	20 (76.92)	13 (50.00)	13 (50.00)	4 (15.38)	22 (84.62)	7 (26.92)	19 (73.08)
Luminal B	21	19 (90.48)	2 (9.52)	17 (80.95)	4 (19.05)	3 (14.29)	18 (85.71)	17 (80.95)	4 (19.05)	10 (47.62)	11 (52.38)	2 (9.52)	19 (90.48)
HER2	21	20 (95.24)	1 (4.76)	14 (66.67)	7 (33.33)	8 (38.10)	13 (61.90)	15 (71.43)	6 (28.57)	9 (42.86)	12 (57.14)	3 (14.29)	18 (85.71)
TNBC	25	20 (80.00)	5 (20.00)	17 (68.00)	8 (32.00)	6 (24.00)	19 (76.00)	21 (84.00)	4 (16.00)	13 (52.00)	12 (48.00)	11 (44.00)	14 (56.00)
X^2		4.437		2.210		3.291		8.627		8.678		8.893	
P		0.218		0.530		0.349		0.035		0.034		0.031	
r		–0.046		0.067		–0.062		0.246		0.258		0.148	

Table 5 Correlation between the KIF15expression of the TNBC and the efficacy of neoadjuvant chemotherapy [*n* (%)]

Variables	*n*	Age		Lymph node involvement		Tumor size (cm)		Clinical effective		Histopathological evaluation	
		> 40	≤ 40	> 0	= 0	> 5	≤ 5	Effective	Ineffective	GPR	PPR
High expression	11	7 (63.64)	4 (36.36)	10 (90.91)	1 (9.09)	5 (45.45)	6 (54.55)	11 (100.00)	0 (0.00)	9 (81.82)	2 (18.18)
Low expression	14	13 (92.86)	1 (7.14)	7 (50.00)	7 (50.00)	1 (7.14)	13 (92.86)	10 (71.43)	4 (28.57)	4 (28.57)	10 (71.43)
P		0.133		0.042		0.056		0.105		0.015	
r		0.363		0.435		0.445		0.387		0.529	

Discussion

Mitotic spindle checkpoint genes were previously considered as targets of anticancer therapies. Studies have shown that taxanes inhibit the proliferation of tumor cells by targeting key components of rivet mitotic spindle-microtubules. As is known, disruption of microtubule assembly is equivalent to inhibition of cell proliferation [9, 10]. Eg5 is one of the key mitotic microtubule motors, and 38 Eg5-targeted therapies, including paclitaxel treatment, have been shown to exert certain anti-tumor effects [13]. However, tumor cell spindles always contribute to resistance and dose restriction whether they are innate or acquired. Therefore, exploring other key spindle components may provide promising targets, which is essential.

Mitotic kinesin, which is a key transducer in cellular mitosis, may act as a novel target with potential roles in cancer therapy. It has been demonstrated that overexpression of tumor-related KIFs is correlated with poorer outcomes in BC patients, and thus, these KIFs can work as potential prognostic biomarkers [14]. KIF15 is a member of the Kinesin superfamily and is usually involved in various biological activities such as endocytotic trafficking, cell signaling, and assembly of cellular structures, and it can also serve as a biomarker of various tumors [15–18]. Interestingly, KIF15 also serves as a functional alternative to Eg5 under defined conditions. Its overlapping functions with these two proteins might lead to the promotion of tumor cell proliferation [15]. Emma [16] reported that the Eg5 blockers K5Is can inhibit mitotic spindle formation; however, in follow-ups, cultured cells were found to be resistant to K5Is. Further studies have suggested that high KIF15 expression is not only related to high migratory activity of tumor cells but also results in the emergence of drug-resistant strains of K5Is. In addition, KIF15 can induce cells to develop into KIF15-dependent K5I drug-resistant strains and adapt to alterations to the cytoarchitecture to break the bottle-neck of tissue development, which is otherwise induced by K5Is. Therefore, it is believed that small-molecule KIF15 inhibitors might enhance the biological activities of K5Is in tumor cells and decrease resistance to paclitaxel and other Eg5 inhibitors. In our previous studies, KIF15 expression in BC tissues was found to be significantly higher than that in tumor-adjacent normal tissues, as determined using tissue microarrays containing 163 BC samples [17–18]. According to the aforementioned findings from the present studies, we consider increased KIF15 expression as a biomarker of high-risk breast tissue and KIF15 expression might also correlate with chemotherapy-resistant breast cancerbe (related to the resistance of taxanes). Thus, KIF15 was selected as the research subject, and we observed the expression status of KIF15 in 93 BC patients receiving NAC to analyze the relationship between the expression of KIF15 and efficacy of NAC and explored the role of this protein in BC development.

Relationships between clinicopathological features in BC and KIF15 expression were observed in our study. The results of Chi-square tests showed higher expression of KIF15, increased numbers of metastatic lymph nodes, and

elevated expression of ER, HER-2, and KI67 ($P < 0.05$), indicating that high KIF15 expression was associated with poor prognosis in BC patients. Conversely, a positive correlation was revealed between KIF15 expression and pCR in BC patients receiving NAC. The efficacy and safety of this 4-cycle NAC regimen of paclitaxel plus cisplatin has been proved in many recent clinical studies [19–20], which is the reason why we choose it as a unified protocol. These results showed that tumors expressing high levels of KIF15 protein were more likely to achieve pCR after NAC. The pathological benefit rate in the high KIF15 expression group was 65.22%, which was significantly higher than that in the low KIF15 expression group ($P < 0.05$). The evaluation results of pathological and clinical benefits remained largely similar. In subgroup analyses, a similar trend was observed in TNBC patients. TNBC patients are the most sensitive to NAC and demonstrated the best pathological and clinical outcomes (84% and 52%) when compared to other subtypes ($P < 0.05$). In our separate analyses involving TNBC cases, patients with lymph node metastasis exhibited elevated KIF15 expression and presented better clinical efficacy outcomes. These results corroborated our previous bioinformatic analysis results based on TCGA database [18].

From this, KIF15 might be suggested as a molecular marker with potential diagnostic and treatment value. Also might become a potential target for reversing the chemoresistance of BC. Nevertheless, our study could not demonstrate the difference of KIF15 expression between various regimen of chemotherapy. Studies have proved that kinesins may contribute greatly to the modulation of breast cancer cell sensitivity to paclitaxel, but not to doxorubicin, carboplatin, or gemcitabine [21–22]. From these experimental results and our review of the literature, we propose that KIF15 might be a promising biomarker for the resistance of taxanes, while the relationship between KIF15 and cisplatin responses remains unknown. Triple-negative tumors,which obtained best efficacy from NAC of all molecular subtypes in our study, however, are known to respond well to carboplatin in previous studies [23–24]. This means we were unable to determine which of these chemotherapeutics singly or together was responsible for the positive effects of the intervention, especially in TNBC. Therefore, more clinical and basic studies are needed in order to find out the possible mechanism of KIF15 inducing chemoresistance and its association between different chemotherapeutic agents. Further follow-ups of survival in the future are also needed to confirm and refine the current results. .

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. McKenna MT, Weis JA, Brock A, *et al*. Precision medicine with imprecise therapy: computational modeling for chemotherapy in breast cance. Transl Oncol, 2018, 11: 732–742.
2. Siegel RL, Miller KD, Fuchs HE, *et al*. Cancer Statistics, 2021. CA Cancer J Clin, 2021, 71: 7–33.
3. Polk A, Svane IM, Andersson M, *et al*. Checkpoint inhibitors in breast cancer-Current status. Cancer Treat Rev, 2018, 63: 122–134.
4. Lydiatt WM, Patel SG, O'Sullivan B, *et al*. Head and neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin, 2017, 67: 122–137.
5. Luketich JD, Pennathur A, Franchetti Y, *et al*. Minimally invasive esophagectomy: results of a prospective phase II multicenter trial-the eastern cooperative oncology group (E2202) study. Ann Surg, 2015, 261: 702–707.
6. Baihong Z, Hongyun Y. Brief introduction of response evaluation criteria in solid tumors. J Int Oncol, 2016, 43: 845–847.
7. Zeng H, Li T, Zhai D, *et al*. ZNF367-induced transcriptional activation of KIF15 accelerates the progression of breast cancer. Int J Biol Sci, 2020, 16: 2084–2093.
8. Wentao Y, Hong B. Expert consensus on pathological diagnosis of breast cancer after neoadjuvant chemotherapy. Chin J Pathol, 2015, 44: 232–236.
9. Yount AL, Zong H, Walczak CE. Regulatory mechanisms that control mitotic kinesins. Exp Cell Res, 2015, 334: 70–77.
10. Wolff AC, Hammond ME, Hicks DG, *et al*. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol, 2013, 31: 3997–4013.
11. Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009, 45: 228–247.
12. Pérez-Melero C. KSP inhibitors as antimitotic agents. Curr Top Med Chem, 2014, 14: 2286–2311.
13. Myers SM, Collins I. Recent findings and future directions for interpolar mitotic kinesin inhibitors in cancer therapy. Future Med Chem, 2016, 8: 463–489.
14. Li TF, Zeng HJ, Shan Z, *et al*. Overexpression of kinesin superfamily members as prognostic biomarkers of breast cancer. Cancer Cell Int, 2020, 20: 123.
15. Kavallaris M. Microtubules and resistance to tubulin-binding agents. Nat Rev Cancer, 2010, 10: 194–204.
16. Sturgill EG, Norris SR, Guo Y, *et al*. Kinesin-5 inhibitor resistance is driven by kinesin-12. J Cell Biol, 2016, 213: 213–227.
17. Sheng J, Xue X, Jiang K. Knockdown of Kinase family 15 inhibits cancer cell proliferation and its Clinical relevance in Triple-Negative Breast Cancer. Curr Mol Med, 2019, 19: 147–155.
18. Sheng J, Li C, Dong M, Jiang K. Identification by Comprehensive Bioinformatics Analysis of KIF15 as a Candidate Risk Gene for Triple-Negative Breast Cancer. Cancer Manag Res, 2020, 12: 12337–12348.
19. Bayarmaa B, Wu Z, Peng J, *et al*. Association of LncRNA MEG3 polymorphisms with efficacy of neoadjuvant chemotherapy in breast cancer. BMC Cancer, 2019, 19: 877.
20. Wu Z, Zhang L, Xu S, *et al*. Predictive and prognostic value of ZEB1 protein expression in breast cancer patients with neoadjuvant chemotherapy. Cancer Cell Int, 2019, 19: 78.

21. Tan MH, De S, Bebek G, *et al*. Specific kinesin expression profiles associated with taxane resistance in basal-like breast cancer. Breast Cancer Res Treat, 2012, 131: 849–858.
22. Singel SM, Cornelius C, Zaganjor E, *et al*. KIF14 promotes AKT phosphorylation and contributes to chemoresistance in triple-negative breast cancer. Neoplasia, 2014, 16: 247–256.
23. Sharma P, López-Tarruella S, García-Saenz JA, *et al*. Pathological Response and Survival in Triple-Negative Breast Cancer Following Neoadjuvant Carboplatin plus Docetaxel. Clin Cancer Res, 2018, 24: 5820–5829.
24. Loibl S, Weber KE, Timms KM, *et al*. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol, 2018, 29: 2341–2347.

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