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Elevated expression of MTDH predicts better prognosis of locally advanced HER-2 positive breast cancer patients receiving neoadjuvant chemotherapy plus trastuzumab

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Abstract

Metadherin (MTDH), also known as astrocyte elevated gene-1 (AEG-1), is an oncoprotein closely related to the development of breast cancer. However, few studies have been done on the expression and clinical significance of MTDH in human epidermal growth factor receptor-2 (HER-2) positive breast cancer patients.

This study aimed to investigate the expression of MTDH in locally advanced HER-2 positive breast cancer, and evaluate the clinical significance of MTDH in predicting the prognosis of patients with HER-2 positive advanced breast cancer who received the neoadjuvant chemotherapy plus trastuzumab.

In 144 HER-2 positive breast cancer tissues, 79 cases showed high expression of MTDH and 65 cases showed low expression. The expression of MTDH in locally advanced HER-2 positive breast cancer tissues was correlated with TNM stage, lymph node metastasis, Miller-Payne (MP) grade, and pathologic complete response (pCR) status ($P < .05$), but was not correlated with patient age, estrogen receptor (ER) expression level, progesterone receptor (PR) expression level, and Ki-67 expression level ($P > .05$). Kaplan–Meier univariate analysis revealed a negative correlation between MTDH expression and the disease-free survival (DFS) and overall survival (OS) in the post-operative patients with locally advanced HER-2 positive breast cancer (log rank test: $P < .001$). By using the COX proportional hazard regression model, it was found that MTDH expression, TNM stage, lymph node metastasis, and Ki-67 expression were closely related to DFS in patients. The hazard ratio (HR) of high MTDH expression was 1.816 (95% CI: 1.165–2.829). In addition, MTDH expression, TNM stage, and lymph node metastasis were also closely related to the OS of patient. The HR of the high expression of MTDH was 2.512 (95% CI: 1.472–4.286). The expression of MTDH in tumor tissues of patients with HER2-positive locally advanced breast cancer was significantly elevated, which was related to the poor pathological features.

High MTDH expression was closely correlated with poor prognosis of patients and was an important factor affecting tumor progression.

Abbreviations: AEG-1 = astrocyte elevated gene-1, ER = estrogen receptor, IHC = immunohistochemistry, MTDH = metadherin, ORR = objective response rate, PR = progesterone receptor.

Keywords: breast cancer, HER-2, MTDH, neoadjuvant chemotherapy

1. Introduction

Breast cancer currently ranks second in the global incidence of malignant tumors, and ranks first in female malignant tumors, thus breast cancer is a serious threat for women's health.[1] At present, neoadjuvant chemotherapy has been widely used in treatment of breast cancer patients, and its advantage is to obtain the opportunity for downgrading of surgery from mastectomy to breast-conserving operation in clinical practice. Overexpression of human epidermal growth factor receptor-2 (HER-2) is closely correlated with the occurrence and development of breast cancer, and it is one of the most well-studied breast cancer driver genes. Currently, a variety of commercial drugs targeting HER-2 have been developed, among which trastuzumab (trade name: Herceptin) is the most widely used one in clinical practice, with impressive therapeutic effects. Trastuzumab combined with neoadjuvant chemotherapy has been shown to significantly improve the prognosis of patients with HER-2 positive breast cancer in clinical trials.[2]

Metadherin (MTDH), also known as astrocyte elevated gene-1 (AEG-1), is an oncoprotein closely related to the development of various cancers. For instance, MTDH is vital for the TNFAIP2-derived EMT process in urothelial cancer cells.[3] Meanwhile,

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Data available upon request.

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MTDH can regulate the proliferation, colony formation, migration and invasion ability in colorectal cancer by governing the activation of PTEN/Akt pathway.[4] In addition, MTDH can regulate the NF-κB pathway to affect the proliferation and metastasis ability in gastric cancer.[5] For breast cancer, high expression of MTDH is closely correlated to the its progression.[6] Notably, numerous studies have reported that MTDH is closely related with the epithelial-mesenchymal transition (EMT) process in different cancers, such as head and neck squamous cell carcinoma, non-small cell lung cancer and nasopharyngeal carcinoma, etc.[7–9] Since EMT is obviously correlated with chemotherapy and trastuzumab resistance,[10,11] high expression of MTDH may lead to poor response to chemotherapy treatment in the patients receiving chemotherapy and trastuzumab. Our previous study has revealed that overexpression of MTDH was significantly correlated with paclitaxel resistance in breast cancer.[12] Up to now, there are few studies on the expression and clinical significance of MTDH in HER-2 positive breast cancer patients. MTDH could mediate the resistance of breast cancer cells against trastuzumab through NF-κB-dependent pathways.[13] However, there is no report on the role of MTDH in prognosis of patients with locally advanced HER-2 positive breast cancer who received neoadjuvant chemotherapy with trastuzumab. We analyzed the relationship between MTDH expression and clinical features and prognosis of patients by retrospectively studying the expression of MTDH protein in tumor tissues of patients with locally advanced HER-2 positive breast cancer, aiming at investigating the role of MTDH in in HER-2 positive breast cancer. Our study will provide experimental evidence for improving the treatment effect of patients.

2. Materials and methods

2.1. Patients and information

All clinical samples were collected from 144 patients (age ranged from 26–74, with a median age of 49, mean age of 48.42 ± 10.15) with locally advanced HER-2 positive breast cancer who were treated with trastuzumab plus neoadjuvant chemotherapy from January 2011 to July 2017 at West China Hospital of Sichuan University and the Fourth Hospital of Hebei Medical University. All patients were confirmed to be invasive carcinoma by core needle biopsy before chemotherapy, and chest CT, upper abdominal CT, skull CT and bone scan were performed to rule out distant metastasis. Before chemotherapy, all patients were examined with bilateral mammography and bilateral breast ultrasound, as well as the examination of draining lymph node before chemotherapy. The size of breast tumor and whether there was axillary lymph node metastasis were determined by breast magnetic resonance imaging (MRI). The patients were staged according to the 7th edition of AJCC staging system, and 8 cases were stage I, 40 cases were stage II, and 96 cases were stage III. A database was established and telephone follow-up was performed every 2 months after surgery and the database was updated. The final follow-up time was November 2018. Data collection was approved by the medical ethics committee of West China Hospital of Sichuan University and the Fourth Hospital of Hebei Medical University. The patients were consented and signed informed consent. All data are available upon request.

2.2. Immunohistochemistry (IHC)

For the breast cancer tumor tissues that were performed with hollow core needle before treatment, the expression of estrogen receptor (ER), progesterone receptor (PR) and Ki-67 was detected by IHC. ER or PR was considered to be positive when ≥1% tumor cells were stained. Low expression of Ki-67 was defined as <14%, and high expression of Ki-67 was defined as ≥14%. MTDH criteria: the yellow or brown staining in the cell membrane or cytoplasm was considered as positive staining. The positive expression grade was scored with semi-quantitative double-score method: no positive cells was recorded as 0; positive cells less than 33% was recorded as 1; positive cells between 33% to 66% was recorded as 2; positive cells more than 66% was recorded as 3. Colorimetric scoring: the strongest part of the expression under high power lens (10×40) was selected and scored according to the color rendering degree. The color similar to the background was recorded as 0; slight color rendering but slightly higher than the background was recorded as 1; Moderate color rendering but significantly higher than the background was recorded as 2; strong staining and showed dark brown was recorded as 3. The total score was calculated by adding the above two scores. Zero was indicated as "-"; score between 1 and 2 was indicated as "+; score between 3 and 4 was indicated as "+ +", and score between 5 and 6 was indicated as "+++". Each section was interpreted by 2 pathologists. When a dispute arose, the third pathologist performed the final interpretation.

2.3. Treatment regimens

According to the NCCN guidelines, all patients received paclitaxel-based neoadjuvant chemotherapy, including paclitaxel/carboplatin/trastuzumab group and sequential use of anthracycline followed by paclitaxel + trastuzumab group. Trastuzumab was administered as following: the initial loading dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 minutes IV infusion every 3 weeks. Surgery was performed within 1 to 2 weeks after completion of 4 to 8 cycles of neoadjuvant chemotherapy.

2.4. Criteria for efficacy evaluation

Treatment efficacy was evaluated every 2 treatment periods. Efficacy evaluation was performed according to RECIST criteria: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Pathologic complete response (pCR) was defined as no residual invasive cancer cells in primary tumors and regional lymph nodes, and residual carcinoma in situ was also included in the pCR group. Miller-Payne (MP) grading was performed according to the consensus of pathological diagnosis after neoadjuvant chemotherapy for breast cancer and classified into MP 1 to 5. The objective response rate (ORR) included CR and PR.

2.5. Statistical analysis

The statistical analysis was performed using SPSS 25.0 statistical software. The correlation of protein expression was compared by chi-square test. All the statistics were tested by 2-tailed test. The significance of MTDH in the prognosis of patients with locally advanced HER-2 positive breast cancer was analyzed by Kaplan–Meier test and COX proportional hazards regression model. $P < .05$ indicates that the difference was statistically significant.

3. Results

3.1. Relationship between expression of MTDH and clinical features in patients with locally advanced HER-2 positive breast cancer

First, we detected the protein expression of MTDH in locally advanced HER-2 positive breast cancer tissues with IHC to

determine its clinical significance. The IHC staining of MTDH protein in these tissues were mostly located on the cell membrane, and a few were found in the cytoplasm (Fig. 1). Of the 144 breast cancer tissues, 79 (54.86%) showed high expression of MTDH protein and 65 (45.14%) showed low expression of MTDH protein. As shown in Table 1, MTDH expression in locally advanced HER-2 positive breast cancer tissues was not correlated with patient age, ER expression level, PR expression level, and Ki-67 expression level ($P=.772$, $P=.856$, $P=.961$, $P=.413$). In addition, there was no difference in MTDH expression between patients receiving 2 different chemotherapy treatment ($P=.439$), and the MTDH expression was correlated with TNM staging, lymph node metastasis, MP grading, and whether achieved pCR ($P=.044$, $P=.016$, $P<.001$, $P<.001$). These results indicated that high expression of MTDH was closely related to the higher clinical grade and lower rate of pCR among the patients with locally advanced HER-2 positive breast cancer.

3.2. The correlation between MTDH expression and the therapeutic effects of neoadjuvant chemotherapy plus trastuzumab

We analyzed the ORR before operation according to the RECIST standard, aiming at evaluating the potential effect of MTDH on the therapeutic effects of trastuzumab plus neoadjuvant chemotherapy in locally advanced HER-2 positive breast cancer patients. The results showed that the ORR rate of the patients with high MTDH expression was significantly lower than that of those with low MTDH expression (76.92% vs 91.14%, $P=.018$; Table 2). Meanwhile, the difference in the tumor size (presented as maximum diameter, measured with MRI) between the patients with high MTDH expression and those with low MTDH expression was not significant before treatment (3.86 ± 0.87 mm vs 3.79 ± 0.91 mm, $P=.644$). However, after the preoperative treatment with trastuzumab plus neoadjuvant chemotherapy, the difference in tumor size was statistically significant, and the patients with low MTDH expression showed smaller tumor size than those patients with high MTDH expression (2.87 ± 0.79 mm vs 2.44 ± 0.71 mm, $P=.002$). These data indicated that the patients with high MTDH expression may benefit less from the combined treatment of neoadjuvant chemotherapy plus trastuzumab.

Table 1

Correlations between the MTDH protein expression level and the clinical parameters of patients with locally advanced HER-2 positive breast cancer.

Clinical parameters	Total	Positive MTDH expression (n)	Negative MTDH expression (n)	*P*
Age				
≤40	36	17	19	.772
>40	108	48	60	
TNM stage				
I+II	48	16	32	.044
III	96	49	47	
Lymph node metastasis				
Low	60	20	40	.016*
High	84	45	39	
ER				
Positive	61	27	34	.856
Negative	83	38	45	
PR				
Positive	69	31	38	.961
Negative	75	34	41	
Ki-67				
≤14%	38	15	23	.413
>14%	106	50	56	
MP grade				
1	46	28	18	<.001*
2+3	45	10	35	
4+5	53	27	26	
pCR				
Reached	109	61	48	<.001*
Not reached	35	4	31	
Chemotherapy method				
AC-TH	68	33	35	.439
TCH	76	32	44	

3.3. Prognostic role of MTDH expression in patients with locally advanced HER-2 positive breast cancer receiving neoadjuvant chemotherapy plus trastuzumab

To further evaluate the clinical significance of MTDH in patients with locally advanced HER-2 positive breast cancer receiving neoadjuvant chemotherapy plus trastuzumab, we used survival

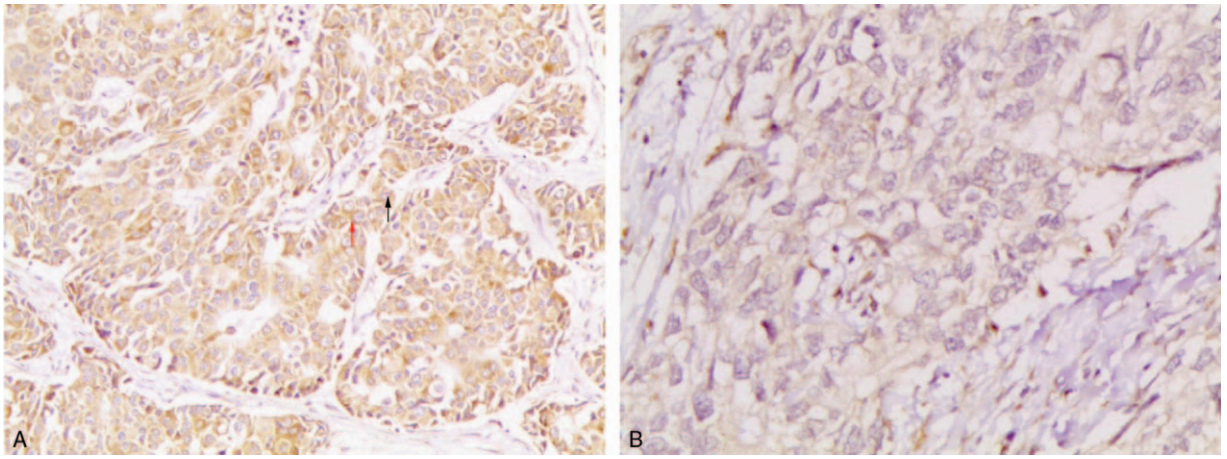

Figure 1. Expression of MTDH in tumor tissues of patients with locally advanced HER-2 positive breast cancer. (A) Positive expression of MTDH. Red arrow pointed to the MTDH expression on cell membrane, and black arrow pointed to the MTDH expression in the cytoplasm. (B) Negative expression of MTDH.

Table 2

Correlation between ORR and MTDH expression status in patients with locally advanced HER-2 positive breast cancer.

	Positive expression of MTDH (n)	Negative expression of MTDH (n)	*P*
CR + PR	50	72	.018*
SD + PD	15	7	

analysis to determine the correlation between MTDH expression and prognosis. Kaplan–Meier univariate analysis revealed that MTDH expression was closely correlated with postoperative DFS and OS after surgery in the patients with locally advanced HER-2 positive breast cancer, and patients with high expression of MTDH had a poor prognosis (Fig. 2, log rank test: $P < .001$). The average DFS was 45.46 ± 2.81 months for patients with low expression of MTDH, and the median DFS was 35 months. The mean DFS was 29.25 ± 1.38 months for patients with high expression of MTDH and the median DFS was 26 months. In addition, the mean OS of patients with low expression of MTDH was 57.36 ± 2.32 months, and the median OS was 54 months, whereas the mean OS of patients with high expression of MTDH was 42.91 ± 1.16 months, and the median OS was 44 months.

By including age, TNM stage, lymph node metastasis, ER expression, PR expression, Ki-67 expression, MP grade, postoperative pCR status, chemotherapy regimen, and MTDH expression, COX proportional hazards regression model analysis revealed that MTDH expression, TNM stage, lymph node metastasis and Ki-67 were correlated with DFS in patients, and the HR value of MTDH with high expression was 1.816 (95% CI: 1.165–2.829). In addition, MTDH expression, TNM stage and lymph node metastasis were correlated with OS of patients, and HR of MTDH with high expression was 2.512 (95% CI: 1.472–4.286). These results revealed that elevated expression of MTDH predicts poor prognosis for patients with locally advanced HER-2 positive breast cancer receiving neoadjuvant chemotherapy plus trastuzumab.

4. Discussion

In recent years, the overall therapeutic effect of breast cancer has been significantly improved, benefiting from the advancement of cancer comprehensive treatment methods including surgery, radiotherapy, chemotherapy, endocrine therapy, and targeted therapy. However, the overall treatment effect of breast cancer is still not satisfying. Neoadjuvant chemotherapy is a chemotherapy strategy applied before surgery aiming at reducing tumor volume and metastatic lymph node metastasis, and improve surgical cure rate.[14] HER-2 is one of the most well-studied breast cancer driver genes. The HER-2-targeted drug trastuzumab combined with neoadjuvant chemotherapy has been shown to significantly improve the prognosis of patients with HER-2 positive breast cancer.[15] However, further studies are needed to investigate the factors that affect the therapeutic effect of trastuzumab in clinic in order to further improve the prognosis of patients.

MTDH is an oncoprotein that is widely involved in the malignant biological behavior of various tumors, and can affect tumor cell proliferation, apoptosis, invasion, metastasis, angiogenesis, etc.[12,16] Subsequent studies have found that MTDH is also involved in the resistance of a variety of chemotherapeutic drugs, including cisplatin, doxorubicin, 5-fluorouracil and paclitaxel.[16–18] In tumors, MTDH can activate a variety of signaling pathways, such as NF-κB, PI3K/AKT, Wnt/β-catenin, MAPK, etc.[19–21] Emdad et al demonstrated that MTDH was highly expressed in breast cancer, which could promote breast cancer cell proliferation and invasion ability.[22] With the increasing importance of molecular typing in the diagnosis and treatment of breast cancer, the expression and significance of MTDH in different tumor molecular types have gradually been elucidated. Liu et al found that in triple-negative breast cancer, high expression of MTDH promoted proliferation and metastasis of breast cancer cells,[23] while Tokunaga et al found that MTDH was lowly expressed in breast cancer patients with high ER and/or PR expression.[24] However, there are still few reports on the expression of MTDH as well as its prognostic significance in HER-2 positive breast cancer, especially in the study of neoadjuvant chemotherapy combined with trastuzumab. The present study revealed that in patients with locally advanced HER-2 positive breast cancer, high expression of MTDH was positively correlated with TNM stage and lymph node metastasis, indicating that MTDH was closely related to the progression of HER-2 positive breast cancer. In addition, it is worth noting that MTDH expression was not correlated with ER and PR expression in this study, suggesting that expression of MTDH was not correlated with ER and PR in HER-2 positive breast

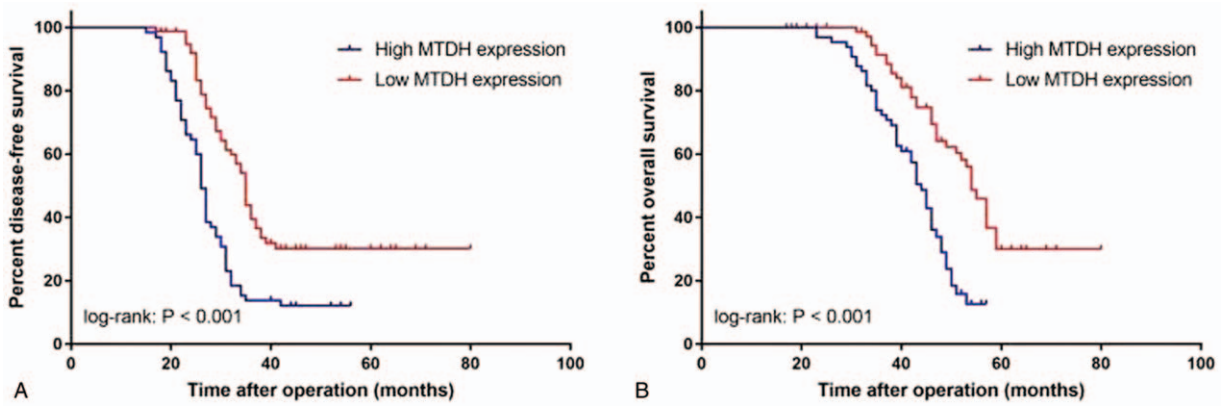

Figure 2. Prognostic significance of MTDH in patients with locally advanced HER-2 positive breast cancer receiving neoadjuvant chemotherapy plus trastuzumab. (A) Relationship between MTDH expression and DFS. (B) Relationship between MTDH expression and OS.

Table 3

Relationship between clinical features of locally advanced HER-2 positive breast cancer and patients DFS.

Clinical Parameters	Median DFS	HR	95% CI	P
Age		1.233	0.763 – 1.990	.392
≤40	31			
>40	30			
TNM stage		2.289	1.452 – 3.610	<.001*
I+II	39			
III	27			
Lymph node metastasis		3.365	2.060 – 5.496	<.001*
Low	35			
High	27			
ER		0.674	0.386 – 1.176	.165
Positive	32			
Negative	28			
PR		1.313	0.750 – 2.299	.340
Positive	31			
Negative	30			
Ki-67		1.713	1.037 – 2.829	.036*
≤14%	32			
>14%	29			
MP grade		1.210	0.958 – 1.527	.109
1	29			
2+3	33			
4+5	28			
pCR		0.618	0.339 – 1.125	.115
Reached	36			
Not reached	29			
Chemotherapy method		0.881	0.585 – 1.328	.545
AC-TH	30			
TCH	30			
MTDH expression		1.816	1.165 – 2.829	.008*
High	26			
Low	35			

Table 4

Relationship between clinical features of locally advanced HER-2 positive breast cancer and patients OS.

Clinical Parameters	Median OS	HR	95% CI	P
Age		0.837	0.482–1.451	.526
≤40	46			
>40	49			
TNM stage		2.958	1.751–4.996	<.001*
I+II	57			
III	45			
Lymph node metastasis		2.595	1.547–4.356	<.001*
Low	59			
High	46			
ER		0.856	0.480–1.525	.597
Positive	49			
Negative	46			
PR		1.087	0.625–1.893	.767
Positive	48			
Negative	47			
Ki-67		1.398	0.762–2.565	.279
≤14%	51			
>14%	47			
MP grade		0.996	0.788–1.259	.973
0	46			
1+2	54			
3+4	49			
pCR		0.593	0.303–1.164	.129
Reached	59			
Not reached	46			
Chemotherapy method		0.756	0.475–1.201	.236
AC-TH	46			
TCH	49			
MTDH expression		2.512	1.472–4.286	.001*
High	44			
Low	54			

HR = hazard ratio.

cancer patients. Witzel et al found that the addition of trastuzumab significantly increased the pCR rate in HER-2 positive breast cancer patients receiving neoadjuvant chemotherapy.[25] This study found that high expression of MTDH was correlated with low pCR rates in patients with locally advanced HER-2 positive breast cancer who received trastuzumab plus neoadjuvant chemotherapy, suggesting that MTDH was closely correlated with the progression of HER-2 positive breast cancer. Du et al found that MTDH could inhibit PTEN expression through NF-κB-dependent pathway and result in breast cancer cells resistant to trastuzumab.[13] We found that the DFS and OS in high MTDH expression group were shorter than that in low MTDH expression group in patients with locally advanced HER-2 positive breast cancer who received trastuzumab combined with neoadjuvant chemotherapy, which provided clinical evidence for the study of MTDH on anti-drug resistance of trastuzumab. Recently, Tian et al found that lobaplatin could inhibit breast cancer cell proliferation and induce apoptosis by down-regulating MTDH expression.[26] Therefore, the addition of lobaplatin in neoadjuvant chemotherapy combined with trastuzumab is likely to further improve the treatment of patients with locally advanced HER-2 positive breast cancer with high expression of MTDH Tables 3 and 4.

5. Conclusions

In summary, high expression of MTDH in tumor tissues of patients with locally advanced HER-2 positive breast cancer is closely correlated to higher TNM stage and more lymph node metastasis, which may lead to shorter DFS and OS. Due to the important role of MTDH in chemotherapy and anti-HER-2 treatment, it is possible that MTDH maybe a new therapeutic target for breast cancer. Taken above, the treatment combined with MTDH targeting may further enhance the efficacy of neoadjuvant chemotherapy combined with trastuzumab and improve the prognosis of patients.

Author contributions

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