Influencing Factors of Bone Metastasis in Human Epidermal Growth Factor Receptor 2 Negative Breast Cancer and Efficacy of Capecitabine Plus Docetaxel

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Zhang *et al.*: To Investigate the Influencing Factors of Bone Metastasis

The clinical data characteristics of human epidermal growth factor receptor 2 negative breast cancer patients were analyzed to investigate the influencing factors of bone metastasis. A total of 754 patients with human epidermal growth factor receptor 2 negative breast cancer admitted to the First People's Hospital of Lianyungang from January 2017 to September 2022, including 273 patients in the bone metastasis group and 481 patients in the non-bone metastasis group, were retrospectively and systematically evaluated for their clinic pathological characteristics, treatment modalities and their influencing factors. Chi-square test and Mann-Whitney U test were used to calculate the differences in clinical data between patients with human epidermal growth factor receptor 2 negative bone metastases and those without bone metastases. Binary logistic regression was performed to analyses the risk factors for the development of bone metastases in human epidermal growth factor receptor 2 negative breast cancer. A significant difference was found between the patients in the bone metastasis group and the non-bone metastasis group in terms of T-stage, N-stage, estrogen receptor, progesterone receptor, tumour molecular classification, axillary lymph node metastasis and quality of life scores (functional assessment of cancer therapy-breast) after combined therapy with capecitabine plus docetaxel (Z=-2.706, Z=-2.864, χ^2=75.954, χ^2=55.618, χ^2=114.854, χ^2=305.211, χ^2=66.945 and p<0.05), while statistical significance was absent in terms of age and location of the primary site (χ^2=2.888, χ^2=1.903 and p>0.05). Logistic regression analysis revealed that high T-stage, luminal A molecular staging and the occurrence of axillary lymph node metastases were all risk factors for bone metastases in human epidermal growth factor receptor 2 negative breast cancer patients (OR=4.352, 95 % CI=2.147 to 8.823, p<0.001; OR=0.281, 95 % CI=0.179 to 0.441, p<0.001 and OR=12.766, 95 % CI=6.712 to 24.283, p<0.001). The occurrence of bone metastases in human epidermal growth factor receptor 2 negative breast cancers was statistically correlated with T-stage, N-stage, estrogen receptor, progesterone receptor, molecular tumour staging, axillary lymph node metastasis and patient quality of life scores after combined therapy with capecitabine plus docetaxel. High T-stage, luminal A and axillary lymph node metastasis were all risk factors. Combined therapy of capecitabine and docetaxel provides significant efficacy in patients with human epidermal growth factor receptor 2 negative breast cancer bone metastases.

Key words: Breast cancer, bone metastases, human epidermal growth factor receptor 2 negative, capecitabine, docetaxel

Breast cancer is the most common female malignancy, with approximately 1.7 million new cases of breast cancer reported worldwide each year[1]. Bone metastases, lung metastases and liver metastases develop in more than 75 % of patients with intermediate to advanced breast cancer, with bone metastases being the most common[2-4]. Bone metastases secondary to breast cancer are associated with an array of bone-Skeletal Related Events (SREs) such as pathological fractures, hypercalcemia and persistent bone pain[5]. The median time from diagnosis of bone metastases to the first SRE can be as short as 1.8 mo and the incidence of SREs increases significantly in the first 12 mo after the

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diagnosis of bone metastases[6], resulting in an increased burden of life for breast cancer patients. Cisplatin and paclitaxel are commonly recommended as adjuvant therapy for breast cancer patients in the early stages of the disease. However, their efficacy is unsatisfactory. Capecitabine and docetaxel are clinically effective in affecting nucleic acid synthesis to achieve anti-tumour effects[7]. Thus, accurate prediction of the risk of bone metastasis in breast cancer patients in the short term and more reasonable drug administration for risk control can provide relief to patient's pain and reduce their life and psychological burden. To this end the current research was performed to investigate the influencing factors of bone metastasis. Baseline patient profiles including the a total of 754 patients with Human Epidermal Growth Factor Receptor 2 (HER-2) negative breast cancer admitted to the First People's Hospital of Lianyungang from January 2017 to September 2022, including 273 patients in the bone metastasis group and 481 patients in the non-bone metastasis group with an incidence of bone metastases of 36.21 % were recruited for analysis. The 754 patients were grouped by different factors according to their age (whether they were older than 50 y), primary tumour location, T-stage, N-stage, Estrogen Receptor (ER), Progesterone Receptor (PR), tumour molecular classification (luminal A, luminal B or triple-negative), axillary lymph node metastasis and quality of life score after combined therapy with capecitabine plus docetaxel. Clinical data were recorded, including age, location of the primary breast site, T-stage, lymph node metastasis, ER, PR and other clinical data characteristics. All patients included in the study were given capecitabine plus docetaxel and the statistical association between these factors and the development of bone metastases was investigated according to the presence of a significant improvement in quality of life scores. The clinical indicators and risk factors that predispose patients with this group of breast cancers to bone metastases were analyzed. Data analyses were performed using Statistical Package for Social Science (SPSS) 26.0 statistical software. The differences in clinical data between patients with and without bone metastases were assessed using the Chi-square (χ^2) test and the Mann-Whitney U test. Variables with statistically significant differences were included in a binary logistic regression analysis of factors influencing bone metastases in breast cancer. The test level was 0.050. A significant difference was found between the patients in the bone metastasis group and the non-bone metastasis group in terms of T-stage, N-stage, ER, PR, tumour molecular classification, axillary lymph node metastasis and quality of life scores (Functional Assessment of Cancer Therapy-Breast (FACT-B)) after combined therapy with capecitabine plus docetaxel ($Z=-2.706$, $Z=-2.864$, $\chi^2=75.954$, $\chi^2=55.618$, $\chi^2=114.854$, $\chi^2=305.211$, $\chi^2=66.945$ and $p<0.05$), while statistical significance was absent in terms of age and location of the primary site ($\chi^2=2.888$, $\chi^2=1.903$ and $p>0.05$) as shown in Table 1. Statistically significant case numerical characteristics were included in a binary logistic regression analysis (Table 2), the results of which showed that ER positive, PR positive and high N-stage, though all statistically significant in terms of differences, were not statistically supported as risk factors for bone metastases in HER-2 negative breast cancer. Logistic regression analysis revealed that high T-stage, luminal A molecular staging and the occurrence of axillary lymph node metastases were all risk factors for bone metastases in HER-2 negative breast cancer patients (OR=4.352, 95 % CI=2.147 to 8.823, $p<0.001$; OR=0.281, 95 % CI=0.179 to 0.441, $p<0.001$; OR=12.766, 95 % CI=6.712 to 24.283, $p<0.001$) as shown in Table 2 and Table 3. Studies have shown that bone metastases are the most common type of metastasis from breast cancer and that the risk of bone metastases increases as breast cancer develops over time. Patients with bone metastases present a relatively good prognosis compared to other metastases[8]. Nevertheless, the quality of life of patients decreases as SREs rise, resulting in a significant increase in the burden of life and psychological burden of patients. With the availability of predictive index parameters for bone metastases in HER-2 negative breast cancer, early interventions against the risk of bone metastases are available to avoid the impact of premature bone metastases on the patient's quality of life and to improve the prognosis of the patient's quality of life by employing the most appropriate drugs for different patients with bone metastases. The recommended chemotherapy drugs for breast cancer include anthracycline, paclitaxel and cyclophosphamide. However, recurrence of the disease leads to poor prognosis and renders second-line treatment impractical. Docetaxel is a paclitaxel drug that promotes the polymerization of micro tubulin and inhibits its depolymerization, thereby disrupting the

mitotic formation of tumour cells to exert anti-tumour effects. Capecitabine, a new oral fluorouracil carbonate, activates the conversion of cellular thymidine phosphorylate into 5-fluorouracil, exerting anti-tumour effects with less destructive effects on normal tissue cells[9,10]. In this study, patients receiving capecitabine plus docetaxel showed a more pronounced improvement in quality of life scores in patients with bone metastases than in those without bone metastases. The results suggested that capecitabine plus docetaxel provide marked clinical and prognosis benefits for patients HER-2 negative breast cancer patients with bone metastases. Thus, its clinical use is recommended in the context of drug safety. Novel bone interventions targeting small molecule inhibitors and nanoparticles are highly promising in the near future[11]. Previous results have shown that a primary lesion with a maximum diameter >2 cm, an aspect ratio ≤1, uneven internal echogenicity, poorly defined borders and Adler flow grade II-III are independent risk factors for axillary lymph node metastasis from breast cancer[12,13]. In this study, the analysis of clinical data and information initially identified high T-stage, luminal A and axillary lymph node metastasis as influencing factors for bone metastasis in HER-2 negative breast cancer patients, so as to provide more effective and reliable preventive information for patients without bone metastasis. The limitations of this study include the limited sample size of the case data and the lack of treatment information, including surgical protocols and medication regimens. Thus, future research is required to provide more reliable clinical data. The occurrence of bone metastases in HER-2 negative breast cancer was statistically correlated with T-stage, N-stage, ER, PR, molecular tumour staging, axillary lymph node metastasis and patient quality of life scores after combined therapy with capecitabine plus docetaxel. High T-stage, luminal A and axillary lymph node metastasis were all risk factors. Combined therapy of capecitabine and docetaxel provides significant efficacy in patients with HER-2

TABLE 1: CLINICOPATHOLOGICAL CHARACTERISTICS OF BREAST CANCER PATIENTS WITH AND WITHOUT BONE METASTASES GROUP [n (%)]

Clinical features	Bone metastasis group (n=273)	Non-bone metastasis group (n=481)	Test value	p value
Age				
≤50	130 (47.6)	260 (54.1)	χ^2=2.888	p=0.64
>50	143 (52.4)	221 (45.9)		
Location of primary focus				
Left breast	169 (61.9)	208 (43.2)	χ^2=1.903	p=0.704
Right breast	104 (38.1)	273 (56.8)		
T staging				
T1	26 (9.6)	223 (46.4)	Z=-2.706	p=0.003
T2	182 (66.5)	201 (41.8)		
T3	39 (14.3)	44 (9.1)		
T4	26 (9.6)	13 (2.7)		
N staging				
N0	14 (5.1)	260 (54.1)	Z=-2.864	p<0.001
N1	116 (42.5)	156 (32.4)		
N2	65 (23.8)	52 (10.8)		
N3	78 (28.6)	13 (2.7)		
ER				
Positive	222 (81.3)	234 (48.6)	χ^2 =75.954	p=0.017
Negative	51 (18.7)	247 (51.4)		
PR				
Positive	195 (71.4)	208 (43.2)	χ^2=55.618	p=0.040
Negative	78 (28.6)	273 (56.8)		

Molecular classification of tumour				
Luminal A	182 (65.9)	130 (27.1)		
Luminal B	39 (14.2)	118 (24.5)	χ^2 =114.853	p=0.013
Triple negative	52 (19.8)	233 (48.4)		
Lymph node metastasis				
Axillary lymph node metastasis	247 (90.5)	143 (29.7)	χ^2=305.211	p<0.001
No axillary lymph node metastasis	26 (9.5)	338 (70.3)		
Functional assessment of cancer therapy				
Significant increase	199 (72.6)	227 (47.2)	χ^2= 66.945	p=0.021
No significant increase or decrease	75 (27.4)	254 (52.8)		

TABLE 2: LOGISTIC REGRESSION ANALYSIS VARIABLE ASSIGNMENT

Factor	Variable	Assignment
ER	X_1	Negative=0 and positive=1
PR	X_2	Negative=0 and positive=1
T staging	X_3	T1, T2=0, T3 and T4=1
N staging	X_4	N0=0 and N1-3=1
Molecular tumour classification	X_5	Luminal A=0 and non-luminal A=1
Lymph node metastasis	X_6	No axillary lymph node metastasis=0 and axillary lymph node metastasis=1

TABLE 3: LOGISTIC REGRESSION ANALYSIS OF FACTORS INFLUENCING BONE METASTASES IN HER-2 NEGATIVE BREAST CANCER (n=754)

Variables	Regression coefficient	Standard error	p	OR value	95 % Confidence interval	
					Lower limit	Upper limit
T staging	1.471	0.369	0.000	4.352	2.147	8.823
N staging	0.449	0.436	0.302	1.567	0.667	3.681
ER	-0.088	0.283	0.756	0.916	0.526	1.596
PR	0.353	0.229	0.135	1.423	0.896	2.261
Molecular classification	-1.269	0.328	0.000	0.281	0.179	0.441
Lymphatic metastases	2.547	0.365	0.000	12.766	6.712	24.283

negative breast cancer bone metastases.

Conflict of interests:

The authors declared no conflict of interests.

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