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Interleukin-6 receptor expression in breast cancer with bone marrow secondaries

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ABSTRACT

Metastatic bone marrow is one of the common bone secondary in breast cancer. This study aims to analyze the relationship between breast cancer features and the role of IL, in particular IL-6 in a bone marrow secondary setting. This is a cross-sectional study conducted at a hematology clinic, from July 2020 until June 2021. A total of 52 women with breast cancer metastasis aged between 25-58 years were included. Tumour specimens were cut into 4 mm slices and then put into 10% buffered formalin for 3 hours-6 hours. All the slides were stained automatically. Slides heated by microwave oven for 25 minutes. The mean age was 45.56 years ± 12.39 years. About 73.1% of women had positive HR while 76.9% had negative HER2neu status. In the hazard analysis, we found no significant difference in terms of age, histology, BMI, and lymph node involvement. Significant clinical factors include Positive HR status (OR=5.1), negative HER2neu status (OR=4.2) and size of the tumour (OR=3.25). The positive IL-6 indicates a higher likelihood of bone marrow metastases, which was found to be correlated with raised risk (OR=10.4). Positive HR status, tumour size and positive IL-6 status raise the risk of bone marrow metastasis in breast cancer. IL-6 is a very strong indicator for the prediction of bone marrow metastasis in breast cancer.

Key words: bone marrow metastasis, breast cancer, hormone receptor, IL-6

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INTRODUCTION

Metastatic bone marrow is one of the common bone secondary in breast cancer. This event is often unknown until an advanced stage, which is a sign of poor prognosis. Therefore, it is important to determine the biological predictors of bone metastasis in breast cancer [1]. In breast cancer, many researchers concluded that the ethology factors for the development of breast cancer include hormone receptor expression, breast cancer period, large BMI, large tumour size, lymph node spread, middle age group, histopathology, genetic profile and interleukin expression. Later on, IL has been found as a breast cancer marker progressing and associated with hormonal receptors and HER2neu [2]. However, they have never been clinically investigating the roles in predicting bone marrow metastasis. To support the early detection and management of metastatic breast cancer, it is necessary to establish new biomarkers and predictors for breast cancer metastasis.

This study aims to analyse the relationship between breast cancer features and the role of IL, in particular IL-6 in a bone marrow secondary setting.

METHODS

Study design and setting

This is a cross-sectional study conducted at a haematology clinic, from July 2020 until June 2021. A total of 52 women with breast cancer metastasis aged between 25 years-58 years were included.

Inclusion criteria

- Metastatic breast cancer
- Comprehensive
- Well oriented

Exclusion criteria

- Non-metastatic cases
- Before chemotherapy or surgery
- Women on Herceptin therapy

PROCEDURE

Tumour specimens were cut into 4 mm slices and then put into 10% buffered formalin for 3 hours-6 hours. All the slides were stained automatically. Slides heated by microwave oven for 25 minutes. The scoring format was adapted according to the

International Breast Cancer Study Group [3].

Interleukin-6 preparation

Tumour fragments were sliced into 3 mm paraffin blocks. These were put on slides, then de-paraffinized and re hydrated with alcohols (10%, 20%, 30% and 50%). Then, all slides were incubated with 3% hydrogen peroxidase for ½ hour. Then, added buffered Ethylene-Di-amine-TetraAcetic Acid (EDTA) at 95o C for 35 minutes for pan steam to retrieve the antigen. Then, all slides were cooled. After that, all slides were covered with Bovine Serum Albumin (BSA) solution for ½ hour and kept in the refrigerator. Then, the slides were cleaned with Phosphate-Buffered Saline (PBS) for ¼ hour twice. Using a 3,3′ -di-amino-benzidine tetra-hydrochloride (0.5%) on the slides with hematoxylin for 5 minutes for fixed staining. After staining, all slides were examined by microscope [4].

Statistical analysis

A statistical package for social science (SPSS version 24.0, Chicago: SPSS, Inc.) was used. Results were described in the form of frequencies and percentages for qualitative data and (mean, and SD) calculation for quantitative data. The chi-square test was used to detect the relationship between continuous variables. A one-sided P value of 0.05 or less was considered statistically significant. The Odds Ratio (OR) was used to assess the risk factors of marrow metastasis.

RESULTS

The mean age was 45.56 years ± 12.39 years. The frequent women aged above 50 years (65.4%). About 73.1% of women had positive HR while 76.9% had negative HER2neu status. The prevalent histology was IDC (96.2%). The mean BMI was 24.11 kg/m^2 ± 13.55 kg/m^2 and the mean mass size was 3.21 cm ± 1.75 cm. LAP was seen in 19 cases (54,5%). IL-6 was positive in 35 cases (67.3%).

In the hazard analysis, we found no significant difference in terms of age, histology, BMI and lymph node involvement. Significant clinical factors include Positive HR status (OR=5.1), negative HER2neu status (OR=4.2) and size of the Tumour (OR =3.25). The positive IL-6 indicates a higher likelihood of bone marrow metastases, which was found to be correlated with raised risk (OR=10.4) (Table 1).

DISCUSSION

IL-6 can be used as a biomarker to indicate the bone marrow secondaries in women with advanced breast cancer. It is recommended to examine IL-6 status as a routine prognostic marker. Positive HR status rises the risk of bone marrow secondaries as high as 5 times, while positive IL-6 increases it 10 times. These metastatic events in breast cancer can be attributed to the mutation of HR and HER2neu when circulating cells of the Tumour are spreading to the bone marrows and forming micro-metastatic niches via osteoblasts interaction [5].

Annually, the hazard rates of bone recur in positive hormonal breast cancer continue to flare up to 10 years, whereas visceral recur drops after peaking at 5 years [6]. In some studies, HR expression and LAP are the strongest predictors of slow-onset recurring breast cancer secondaries, especially in bone marrow [5].

Retrospectively, Han and co-authors examined more than 400 women with breast cancer who underwent surgery [7]. They reported breast cancer with positive hormonal receptors has a significant great risk of bone marrow metastasis. Another study by Bartels et al, confirmed that in women with breast cancer, the bone metastases had positive hormone receptor expression [8].

Among the variables investigated in this work, we found that age, histology, BMI and lymph node involvement do not predict bone metastases in breast cancer [9].

A cohort study conducted by Purus Hotham et al, with a sample size of 3,553 females, found that elderly women had a reduced risk of bone marrow metastases [10].

Previously, authors concluded the larger the Tumour size (>5 cm), the more possible bone marrow metastases in breast cancer. A study of the Korean nationwide health insurance database explained that for bone marrow metastasis occurrence, the duration takes place 15 months from the first onset of starting metastasis, as a result, the longer a person has breast cancer, the higher the risk of bone marrow metastases [11, 12].

The novelty of IL-6 as a new biomarker to predict bone marrow metastasis in breast cancer is studied. IL-6 belongs to pro-inflammatory chemokine group, activating multiple intracellular signalling and increasing the expression along with receptors in cancer cells. It has a significant regulatory role in the development of the Tumour [13]. It can immediately stimulate osteogenesis

Tab. 1. Variables and hazards of the study

Variable		n(%)	OR	P value
Age (years)	< 50	18 (34.6)	2.7	0.1
	≥ 50	34 (65.4)		
Hormonal receptors	Positive	38(73.1)	5.1	0.0001
	Negative	14 (26.9)		
HER2neu	Positive	12 (23.1)	4.2	0.005
	Negative	40 (76.9)		
Histopathology	IDC	50 (96.2)	1.9	0.08
	Other	2 (3.8)		
BMI (kg/m^2)	< 25	22 (42.3)	0.55	0.9
	≥ 25	30 (57.7)		
Mass size (cm)	<5	25 (48.1)	3.25	0.05
	≥ 5	27 (51.9)		
LAP	Positive	19 (36.5)	1.85	0.75
	Negative	33 (63.5)		
IL-6	Positive	35 (67.3)	10.4	0.0001
	Negative	17 (32.7)		

and bone resorption *in vivo* in experimental animal model studies [14].

The stem-like cells of breast cancer are an important therapeutic target for antagonized Tumour initiation, maintenance and marrow metastases. IL-6 is up-regulated in these processes and associated with poor prognosis status. It is reported to promote of progression of breast cancer by raising cell invasion, spreading, metastases and angiogenesis. Also, it is up-regulated in HER2neu-positive breast cancers. Moreover, it is an independent prognostic factor for relapsing survival in metastatic breast cancer [3].

CONCLUSION

Positive HR status, Tumour size and positive IL-6 status rise the risk of bone marrow metastasis in breast cancer. IL-6 is a very strong indicator for the prediction of bone marrow metastasis in breast cancer.

COMPETING INTERESTS

None.

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