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Research article

CXCR4 and RANK Combination as a Predictor of Breast Cancer Bone Metastasis in Indonesia

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Abstract

Background: Breast cancer has the highest prevalence and incidence among cancers in women. Moreover, it is the most prevalent among all other cancers in Indonesia. Bone metastasis results in higher incidence, better overall survival, but requires higher-cost treatments than visceral metastasis. Therefore, an early predictor of bone metastasis is needed to make early interventions to be efficiently given. Instead of other biomarkers of bone metastasis, CXCR4 and RANK are highly expressed in breast cancer and correlate with bone metastasis. Hence this study is expected to prove the potential of CXCR4 and RANK combination as a predictor of breast cancer bone metastasis.

Methods: In a case-control study, CXCR4 and RANK immunohistochemistry tests were done in 58 stage I-IV breast cancer Indonesian subjects. Association between marker combinations and incidence of bone metastasis was analyzed. Then, the diagnosis accuracy values were calculated. Moreover, its associations with clinicopathological factors were also examined.

Results: There was a significant association of the highly expressed CXCR4 and RANK combination with bone metastasis (P <0.01). Besides, the combination of CXCR4 and RANK detections resulted in 100% sensitivity and 66% specificity in predicting bone metastasis. Breast cancer's stage was significantly associated with CXCR4 and RANK expressions combination (P<0.01).

Conclusions: A combination of CXCR4 and RANK expressions could act as a screening method to predict the bone metastasis in breast cancer.

Abbreviations

IL-8: Interleukin-8; RANK: Receptor Activator of Nuclear Factor Kappa-B; RANKL: Receptor Activator of Nuclear Factor Kappa-B Ligand; CXCR4: C-X-C Chemokine Receptor Type 4; PTHrP: Parathyroid Hormone-related Protein; B-CTx : Beta-C-Terminal Telopeptide; BM: Bone Metastasis; NBM: Non-Bone Metastasis; IHC: Immunohistochemical; CSLEX-1: Sialyl Lewis X-1 (CSLEX-1) with Cancer Antigen 15-3 (CA 15-3); CA 15-3: Cancer Antigen 15-3; NTx: N-Telopeptide of type I collagen

Introduction

Breast cancer has the highest prevalence and incidence among any other cancers in women [1]. In Indonesia, breast cancer is the most prevalent among all cancer [1,2]. Based on Global Burden of Cancer 2018, the global incidence of breast cancer was around 2,093,876 and the mortality was around 1,761,007. In Indonesia, the incidence was estimated at around 58,256 and the mortality was around 22,692 [1].

Breast cancer frequently metastasizes to bone approximately in 70% of advanced breast cancer patients [3].

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Even though bone metastasis results in a better overall survival rather than visceral metastasis, it gives an enormous burden to the treatment cost. Hence, tumor markers are expected to early predict the bone metastasis [3-5]. This may help early intervention to enhance the quality of life and reduce the treatment cost of the patient.

Many biomarkers were hypothesized to be implicated in breast cancer bone metastasis such as Osteopontin, Osteonectin, Interleukin-8 (IL-8), Receptor Activator of Nuclear Factor Kappa-B (RANK), Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL), C-X-C Chemokine Receptor Type 4 (CXCR4), bone sialoprotein, tumor cell surface's integrin, Fas/Fas ligand, Parathyroid Hormone-related Protein (PTHrP), and Beta-C-Terminal Telopeptide (B-CTx) [6-9]. Among those markers, CXCR4 and RANK are known to have the greatest association with breast cancer bone metastasis, and both are involved in cancer cell's homing to bones [10]. Moreover, CXCR4 and RANK act in the earliest cascade of the bone metastasis process [11]. Hence, this study aims to prove the potential of combined CXCR4 and RANK detections in predicting the bone metastasis occurrence of a breast cancer patient.

Methods

A retrospective case-control study was conducted in a national general hospital. This study had been approved by medical ethics committee of the university. Fifty-eight breast cancer specimens were obtained from an Anatomical Pathology Laboratory between January 2015 to October 2016. Moreover, the consecutive sampling method was used. Paraffin-embedded tissue blocks from stage I-IV breast cancer subjects were divided into two groups based on the presence of bone metastasis (which were confirmed by radiological examinations) within 5 years after initial breast cancer diagnosis (based on data stated in medical record): Bone Metastasis (BM) vs Non-Bone Metastasis (NBM). Paraffin blocks that were damaged in the process or taken from patients with any previous treatment were excluded.

The paraffin-embedded tissue blocks were cut into four µm sections, one tissue section was then stained with Hematoxylin and Eosin to confirm the breast cancer. Two other tissue sections were used for CXCR4 and RANK immunohistochemistry staining. Immunohistochemistry staining was done using an automatic immunohistochemical stainer. Ventana Roche BenchMark XT. CXCR4 GTX22090 (1:100 dilution) and RANK GTX31188 (1:200 dilution) were used as the immunohistochemical markers. Antigen-antibody reactions were visualized by Ultraview Brown Counterstain DAB Detection Kit (Ventana Medical Systems).

All Immunohistochemical (IHC) stains were then examined and scored by experienced breast pathologists. Cells from five random different fields were counted using high magnification.

Positive and negative control specimens for each marker analysis were used in this study for the comparation. Positive controls were breast cancer specimen samples showing both positive marker expressions. Besides, negative controls were specimens prepared through the same procedure but without using the primary antibody.

The following IHC staining scoring is taken and modified from the previous method used in a study by Sun, et al. [12]. The percentage of CXCR4 positive tumor was determined semi-quantitatively as follows: 0 (0%), 1 (1-10% positive cells), 2 (11-50% positive cells), 3 (51-80% positive cells), and 4 (81-100% positive cells). Cytoplasmic staining intensity was classified into 0 (negative), 1 (weak), 2 (moderate), and 3 (strong). Then, the positive cell percentage and staining intensity were multiplied to define a composite score. Composite score was classified into 0 (negative), + (1-4), ++ (5-8), and +++ (9-12). CXCR4 was considered highly expressed if the composite score was ++ or +++ (5-12 score). The intensity of RANK staining was classified into four groups based on a method by Li, et al. including absent (0), positive but less intense (1), same intense (2), and more intense (3) compared to the positive control [13]. A more than 1 staining intensity score in more than 50% of cancer cells was considered as highly expressed. The combination of CXCR4 and RANK expressions was considered high if one or both of the markers were highly expressed.

Besides, the associations of marker expressions with metastasis, menopausal status, cancer stadium, lymph node involvement, hormonal receptor, and HER-2 amplification were also analyzed.

Shapiro-Wilk test was used for normality test, if $P>0.05$ the data distribution was normal and the data would be presented as mean±deviation standard. Otherwise, the data distribution was considered not normal and the data would be presented as median (minimum-maximum). Chi-Square/Fischer-Exact was used for analytical test for comparing BM and NBM group depended on the normality test.

Results

A total of 58 women breast cancer subjects participated in this study. Each of BM and NBM group included 29 subjects. In BM group, 51.7% had menopause, 100% had late-stage breast cancer, 100% had high tumor grade, 65.5% had No Special Type (NST), 72.4% had lymph node involvement, 86.2% were Estrogen Receptor/ Progesterone Receptor (ER/PR) positive, and 62.1% had HER-2 amplification. In NBM Group, 51.7% had menopause, 27.6% had late-stage breast cancer, 93.1% had high tumor grade, 58.6% had NST type, 44.8% had lymph node involvement, 82.6% were ER/PR positive, and 48.3% had HER-2 amplification. The detailed data on the characteristics of subjects are provided in Table 1. The majority of subjects with bone metastasis had highly-expressed CXCR4 and RANK. In contrast, most of the non-bone metastasis subjects showed low expression of both markers. The representative images of immunohistochemistry results are provided in Figures 1,2.

Association of CXCR4 and RANK expressions with breast cancer bone metastasis

High CXCR4, RANK, and CXCR4+RANK expressions were significantly associated with breast cancer bone metastasis ($P<0.01$). Breast cancer subjects with high CXCR4 expressions

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would have 134.4 folds of risk for bone metastasis than low CXCR4 expressions. Meanwhile, breast cancer subjects with high-RANK expressions would have 88 folds of risk for bone metastasis than low-RANK expressions. The results of the analysis of the associations can be seen in Table 2. The authors assessed the diagnostic accuracy of CXCR4, RANK, and CXCR4+RANK expression in breast cancer bone metastasis based on sensitivity, specificity, positive predictive value, and negative predictive value. The results of the calculation on diagnosis accuracy are provided in Table 3. The sensitivity and negative predictive value of the CXCR4+RANK combination was 100% and higher than the values got from the single marker usage. However, the specificity and the positive predictive values of the marker combination were lower than the single marker usage.

Association of clinicopathological features with CXCR4 expression, RANK expression and bone metastasis

The relationship between clinicopathological features and breast cancer bone metastasis was assessed. By using bivariate analysis as shown in Table 4, the authors found a significant relationship between breast cancer staging (P <0.01), lymph node involvement (P =0.03), CXCR4 expression (P <0.01), and RANK expression (P <0.01) with breast cancer bone metastasis. Moreover, the authors analyzed the markers association with clinicopathological factors as provided in Table 5. CXCR4 and RANK were only significantly associated with the stage of breast cancer.

Table 1: Characteristics of subjects.

	BM (n =29)	NBM (n =29)
Age (year)*	50(34-84)	50 (26-86)
Menopause		
Yes	15	15
No	14	14
Stage		
Late (IV)	29	8
Early (I,II,III)	0	21
Grade		
High(2, 3)	29	27
Low (1)	0	2
Tumor type		
NST	19	17
Others	10	12
Lymp node involvement		
Yes	21	13
No	8	16
ER/PR		
Positve	25	24
Negative	4	5
HER-2 amplification		
Positive	18	14
Negative	11	15
CXCR4		
High	28	5
Low	1	24
RANK		
High	28	7
Low	1	22

* median (minimum–maximum)

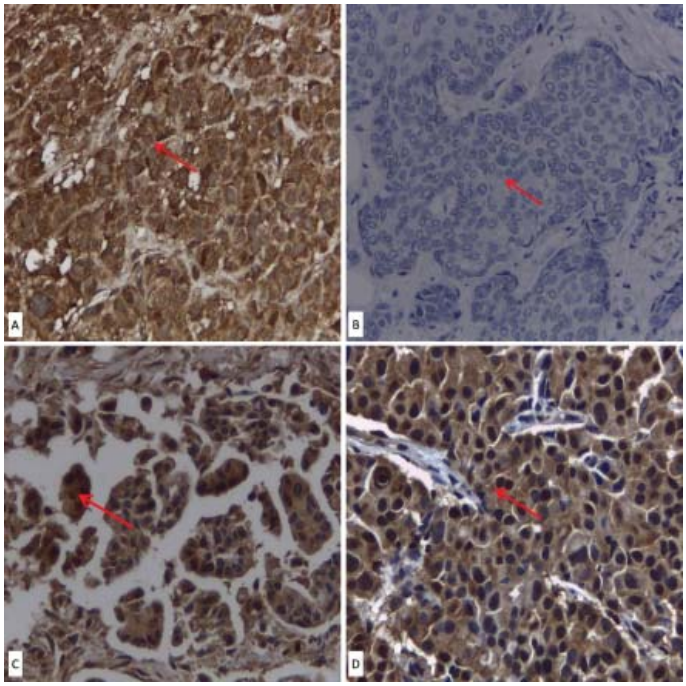

Figure 1: Representative immunohistochemistry images of cytoplasmic CXCR4 expression. Image A: Positive control. Image B: Negative control. Image C: High expression of CXCR4 (5 composite score). Red arrow indicates a strong staining intensity. Image D: Low expression of CXCR4 (4 composite score). Red arrow indicates a moderate staining intensity. Original magnification A, B, C, D 400x.

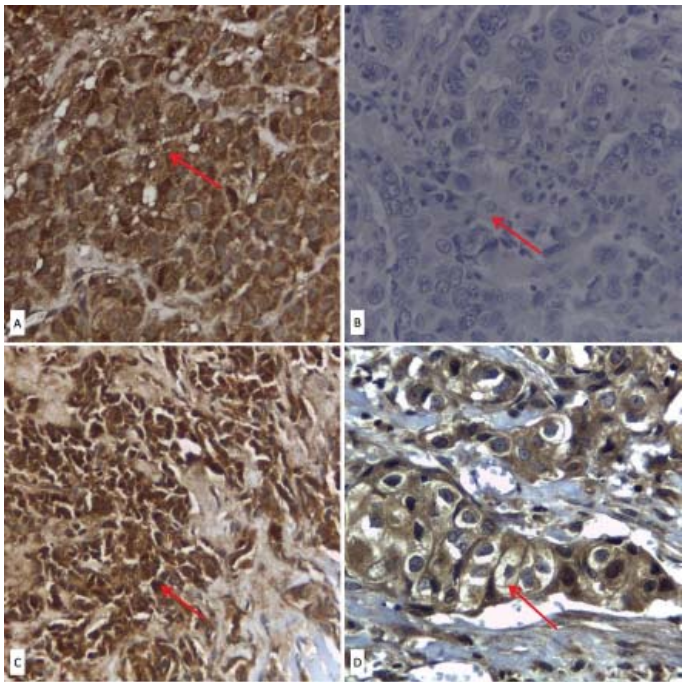

Figure 2: Representative immunohistochemistry images of cytoplasmic RANK expression. Image A: Positive control. Image B: Negative control. Image C: High expression of RANK. Red arrow shows a 2 staining intensity score. Image D: Low expression of RANK. Red arrow shows a 1 staining intensity score. Original magnification A, B, C, D 400x.

Discussion

In the BM group of this study, we found that CXCR4 was highly expressed in 28 (96.6%) subjects and lowly expressed in 1 (3.4%) patient. RANK was highly expressed in 28 (96.6%)

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subjects and lowly expressed in 1 (3.4%) patient. However, in the NBM group, CXCR4 was highly expressed in five (17.2%) subjects and lowly expressed in 24 (82.8%) subjects. RANK was highly expressed in seven ((24.1%) subjects and lowly expressed in 22 (75.9%) subjects. CXCR4 and RANK combination was significantly associated with bone metastasis in breast cancer patients (P <0.001). In this study, CXCR4 has a 97% sensitivity and an 83% specificity, RANK has 97% sensitivity and 76% specificity. Moreover, combined CXCR4 and RANK has 100% sensitivity and 66% specificity as a predictor for bone metastasis. This finding suits Ibrahim, et al. study which stated that combined CXCR4 and RANK expression could be a good predicting factor in breast cancer bone metastasis [10]. For comparison, other previous studies have also proposed other combinations of markers. Washam, et al. reported that the combination of 12-48aa peptide fragment of parathyroid hormone-related protein (PTHrp[12-48]) and N-Telopeptide of type I collagen (NTx) resulted in 86% sensitivity and 95% specificity for the breast cancer bone metastasis detection [14]. Besides, Fujita *et al*. proposed the use of Sialyl Lewis X-1 (CSLEX-1) with Cancer Antigen 15-3 (CA 15-3) which resulted in 45% sensitivity and 95% specificity for detection of breast cancer metastasis, including 34.8% of the positive predictive value on the breast cancer bone metastasis [15].

Table 2: Association between CXCR4 and RANK toward breast cancer BM.

		BM		OR (95%CI)	*P*-value
		(+)	(-)		
CXCR4	High	28	5	134.4	<0.01*
	Low	1	24	(14.7-1231.5)	
RANK	High	28	7	88.0	<0.01*
	Low	1	22	(10.1 – 769.5)	
CXCR4+RANK	High	29	10	-**	<0.01
	Low	0	19		

OR: Odd Ratio
*chi square
**can't be defined, one of the comparison had 0 value

Table 3: Diagnosis accuracy of CXCR4 expression in breast cancer BM.

	Value		
	CXCR4	RANK	CXCR4+RANK
Sensitivity	97%	97%	100%
Specificity	83%	76%	66%
Positive predictive value	85%	80%	74%
Negative predictive value	96%	96%	100%

Table 4: Association between clinicopathological features with breast cancer BM.

	BM	NBM	*P*-value
Stage			
Late (IV)	29	8	<0.01[a]
Early (I,II,III)	0	21	
Grade			
High (2,3)	29	27	0.49[b]
Low (1)	0	2	
Tumor type			
NST	19	17	0.59[a]
Others	10	12	
Lymph node			
Positive	21	13	0.03[a]
Negative	8	16	
ER/PR			
Positive	25	24	1.00[b]
Negative	4	5	
HER-2			
Positive	18	14	0.29[a]
Negative	11	15	
Menopause			
yes	15	15	1.00[a]
no	14	14	
CXCR4			
High	28	5	<0.01[a]
Low	1	24	
RANK			
High	28	7	<0.01[a]
Low	1	22	

[a]Chi Square
[b]Fisher Exact

In this study, there was only a significant association of CXCR4 and RANK combination with the breast cancer stage (P <0.01). A previous study by Shim, et al. reported that high CXCR4 expression was significantly associated with higher histologic grade (P =0.007), younger age (P =0.008), and lower pathologic stage (P =0.045) [16]. Besides, RANK expression was only significantly associated with operation type in a previous study by Park, et al. [17].

The pathogenesis of bone metastasis in breast cancer depends on the "vicious cycle", which describes as the bidirectional tight interaction among breast cancer cells and stromal cells. This regulates the bone niche leading to continuous bone resorption process. An important pathway in the progressivity of breast cancer bone metastasis is RANK-RANKL- Osteoprotegerin (OPG) cascade [3]. These molecules are active in primary cancer cells including in their bone metastasis of breast, hepatocellular, and prostate carcinoma [18].

RANK is a surface receptor commonly found on mature osteoclasts and their progenitors [19]. It induces osteoclastogenesis and controls calcium metabolism. RANKL is a polypeptide which found on the surface of osteoblast and bone stromal cells [10]. It binds to RANK on preosteoclast and mature osteoclast. Signaling through RANK would activate transcription factors, which leads to the differentiation of osteoclast progenitors and limits apoptosis of mature osteoclast [20]. On the other hand, OPG (Osteoprotegerin) prevents the RANK-RANKL interaction on the osteoclast cell membrane [21]. If OPG binds to RANKL, osteoclastogenesis will be inhibited, resulting in bone resorption cessation [21]. However, the RANKL-RANK axis promotes the activation, proliferation, and survival of osteoclast. This stimulates tumorigenesis and metastasis in the bone. Studies reported that breast cancer cell expresses RANK protein on their surface, while RANKL acts as a chemotactic factor of cancer cells [19,20]. A high amount of RANKL within bone microenvironment may stimulate the migration of RANK expressing tumor cells to the bone. In a research by Ibrahim, et al. the positivity of RANK in the primary tumor was always associated with bone relapse [10]. However, 96.6% (28 of 29) of RANK positive subjects had bone metastasis in our study. This might happened because there were 62.1% subjects with HER-2 amplification in the BM group which leads to bigger tendency for visceral metastasis.

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Table 5: Association between clinicopathological features with CXCR4 and RANK expression.

Variable	CXCR4		RANK		CXCR4+RANK		*P*-value CXCR4	*P*-value RANK	*P*-value CXCR4+RANK
	High	Low	High	Low	High	Low			
Stage									
Late (IV)	29	8	31	6	33	4	<0.01[a]	<0.01[a]	<0.01[a]
Early(I,II,III)	4	17	4	17	6	15			
Grade									
High (2,3)	32	24	34	22	38	18	1.00[b]	1.00[b]	1.00[b]
Low (1)	1	1	1	1	1	1			
Tumor type									
NST	21	15	22	14	25	11	0.78[a]	0.88[a]	0.65[a]
Others	12	10	13	9	14	8			
ER/PR									
Positive	28	21	23	11	25	9	1.00[b]	0.18[a]	0.23[a]
Negative	5	4	12	12	14	10			
HER-2									
Positive	19	13	30	19	33	16	0.67[a]	1.00[b]	1.00[b]
Negative	14	12	5	4	6	3			
Lymph node									
Positive	22	12	21	11	22	10	0.15[a]	0.36[a]	0.786[a]
Negative	11	13	14	22	17	9			
Menopause									
yes	17	13	18	12	19	11	0.97[a]	0.96[a]	0.51[a]
no	16	12	17	11	20	8			

[a]Chi Square
[b]Fisher Exact

One of the essential components of bone metastases is the chemotaxis of circulating tumor cells and the stromal cells within the bone environment. CXCR4 is the chemokine receptor used by circulating leukocytes and stem cells for homing to the bone marrow, where an excessive amount of their corresponding chemokine; Stromal Cell-Derived Factor-1 (SDF-1) is present [22,23]. The overexpression of CXCR4 was found in around 30% of primary breast cancer cells, which is proved to mediate cancer cells migrating to target organs, especially where SDF-1α is abundant such as bone [23].

A recent study noted the CXCR4 expression in primary breast cancer was significantly associated with the development of bone metastases [10,24]. Besides, RANK is highly expressed in primary breast cancer [25]. High expression of RANK in breast cancer stimulates migration to the bone which has a high expression of RANKL. Researchers found that predictive accuracy can be further increased with RANK expression [10]. Because both of these markers act in the early cascade of bone metastasis, we hope that these combinations might produce predictive factors with high sensitivity and specificity. In this study, we did not observe OPG because OPG is likely to increase the survival of breast cancer cells that metastasize to the bone environment [26]. The authors also didn't observe RANKL because RANKL presents more abundantly in bone marrow stromal cells [10].

However, a prospective cohort study is needed to evaluate the association of CXCR4 and RANK expressions in early-stage breast cancer and evaluate the prognostic factors. A research for determining the relationship of micro- and macro-metastasis with recurrence or survival is also needed. In each country/region, a study for differences in clinicopathological factors should be determined and compared with the other countries/regions.

Conclusions

In conclusion, a combination of CXCR4 high expression and RANK high expression can act as a predictor for breast cancer bone metastasis. Cancer staging plays an important role in determining CXCR4 and RANK expressions in breast cancer bone metastasis. Therefore, CXCR4 and RANK combination can be used as a screening method to predict bone metastasis in early-stage breast cancer in the future.

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