© 2023 Journal of Pharmacy & Pharmacognosy Research, 11 (6), 926-933, 2023
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres23.1695_11.6.926

Original Article

Check update pattern of tumorigenic vasculature signature based on MMP9 and CXCR4 expression in locally advanced breast cancer

[Comprobación del patrón de actualización de la señal de vasculatura tumorigénica basada en la expresión de MMP9 y CXCR4 en el cáncer de mama localmente avanzado]

Mochamad Bachtiar Budianto[1], Hamzah Sulaiman Lubis[2], Muhammad Luqman Fadli[3], Wiwit Nurwidyaningtyas[4,5*]

[1]Department Oncology of Saiful Anwar General Hospital, Malang 65112, Indonesia.
[2]Department Oncology of Medan Hajj General Hospital, Sumatera Utara 20371,Indonesia.
[3]Department Anatomy Pathology of Saiful Anwar General Hospital, Malang 65112, Indonesia.
[4]Department Molecular and Cellular Biology, Sekolah Tinggi Ilmu Kesehatan Kendedes, Malang, 65126, Indonesia.
[5]Center for Biomedical Research, Research Organization for Health, National Research and Innovation Agency (BRIN), Genomic Building, Cibinong Science Center, Jl. Raya Bogor No. 490, Cibinong – Bogor Km. 46, Bogor, West Java, Indonesia.
*E-mail: wiwi026@brin.go.id

Abstract

Context: Locally advanced breast cancers (LABC) are the most common women malignant tumors. Appropriate vasculature is required for tumor growth support, formed by involving protein signaling, including matrix metalloprotein 9 (MMP9) and C-X-C chemokine receptor type 4 (CXCR4). Neoadjuvant chemotherapy (NAC) administration to inoperable LABC commonly exhibits a positive response, although recurrences may be encountered in a few cases.

Aims: To evaluate the MMP9 and CXCR4 expression shifting after the NAC procedure to establish evidence of the anti-angiogenic effect of NAC, which encourages knowledge of tumor size reduction pathways in LABC.

Methods: Observational designs were conducted in this study. Tissue specimens before and after NAC were collected from 45 LABC-enrolled subjects. The targeted protein expression was analyzed by immunohistochemistry, and stained sections were classified according to the percentage of nuclear-stained tumor cells. Clinicopathological features of LABC were recorded. Tumor size was measured by Vernier caliper before and after NAC.

Results: The results showed the nuclear expression of MMP9 and CXCR4 protein were observed in all tissue specimens. The expression of MMP9 and CXCR4 tended to decrease after the NAC but was not statistically significant for MMP9. There was a significant correlation between expression levels of CXCR4 and tumor size reduction ($p<0.001$) but not for MMP9.

Conclusions: The results of this study demonstrate the anti-angiogenic effect of NAC by inhibiting MMP9 and CXCR4, which may be integrated with tumor size reduction in LABC. Further studies are required to highlight the possibility of recurrence following inhibition of MMP9 and CXCR4 by NAC.

Keywords: breast cancers; CXCR4; MMP9; neoadjuvant chemotherapy; positive response.

Resumen

Contexto: Los cánceres de mama localmente avanzados (LABC) son los tumores malignos femeninos más frecuentes. Se requiere una vasculatura adecuada para el soporte del crecimiento tumoral, formada por la implicación de la señalización de proteínas, incluyendo la metaloproteína de matriz 9 (MMP9) y el receptor de quimioquinas C-X-C tipo 4 (CXCR4). La administración de quimioterapia neoadyuvante (NAC) al LABC inoperable suele mostrar una respuesta positiva, aunque en algunos casos pueden producirse recidivas.

Objetivos: Evaluar el cambio de expresión de MMP9 y CXCR4 tras el procedimiento NAC para establecer evidencias del efecto antiangiogénico de la NAC, lo que favorece el conocimiento de las vías de reducción del tamaño tumoral en el LABC.

Métodos: En este estudio se realizaron diseños observacionales. Se recogieron muestras de tejido antes y después de la NAC de 45 sujetos inscritos en el LABC. La expresión de la proteína diana se analizó mediante inmunohistoquímica, y las secciones teñidas se clasificaron según el porcentaje de células tumorales teñidas nuclearmente. Se registraron las características clinicopatológicas del LABC. El tamaño del tumor se midió con un calibre Vernier antes y después de la NAC.

Resultados: Los resultados mostraron la expresión nuclear de las proteínas MMP9 y CXCR4 en todas las muestras de tejido. La expresión de MMP9 y CXCR4 tendió a disminuir tras la NAC, pero no fue estadísticamente significativa para MMP-9. Se observó una correlación significativa entre los niveles de expresión de CXCR4 y la reducción del tamaño del tumor ($p<0,001$). Hubo una correlación significativa entre los niveles de expresión de CXCR4 y la reducción del tamaño del tumor ($p<0,001$), pero no para MMP9.

Conclusiones: os resultados de este estudio demuestran el efecto antiangiogénico de la NAC mediante la inhibición de MMP9 y CXCR4, que puede integrarse con la reducción del tamaño tumoral en el LABC. Se requieren más estudios para poner de relieve la posibilidad de recurrencia tras la inhibición de MMP9 y CXCR4 por NAC.

Palabras Clave: cánceres de mama; CXCR4; MMP9; quimioterapia neoadyuvante; respuesta positiva.

ARTICLE INFO
Received: May 23, 2023.
Accepted: September 1, 2023.
Available Online: September 15, 2023.

AUTHOR INFO
ORCID: 0000-0001-5833-0465 (MBB)
0000-0002-8285-264X (MLF)
0000-0003-4472-4388 (WN)

Abbreviations: ACS: American cancers society; CNB: core needle biopsy; CXCR4: C-X-C chemokine receptor type 4; CXCL12: HER2, human epidermal growth factor receptor 2; LABC: locally advanced breast cancer; MAPK: mitogen-activated protein kinase; MMP: matrix metalloprotein; NAC: neoadjuvant chemotherapy; PI3K: phosphoinositide-3-kinase; SDF-1: stromal-derived-factor-1.

INTRODUCTION

The successful interaction of cancer cells with their microenvironment is a key feature of neoplasm growth, potentially targeted in cancer treatment. Breast cancer is a preventable malignancy, the leading cause of death in women worldwide. Ineffective early detection elevates advanced-stage findings (Gogia et al., 2018). The American Cancers Society (ACS) reports that 99% of breast cancers diagnosed do not spread, and 86% of breast cancer spread to local tissues or lymph nodes, referred to as locally advanced breast cancer (LABC) feature, which is generally an inoperable presentation (ACS, 2021; Aebi et al., 2022). Multidisciplinary approach for LABC generally includes the administration of neoadjuvant chemotherapy to reduce tumors, as well as mastectomy for LABC with smaller tumor sizes (Balogun and Formenti, 2015; Korde et al., 2021; Masood, 2016). Recurrence, poor prognosis, and low survival rates are accepted clinical problems in LABC (Dhanushkodi et al., 2021).

Rapid proliferation, an abundance of cancer stem cells in the circulation, and metastasis contribute to the recurrence and therapeutic resistance in breast cancer. The complex manner of several protein interactions creates a tumor microenvironment to support oxygen and nutrient supply that are essential for accelerating tumor growth (Larionova et al., 2021). Current cancer treatments are designed to inhibit cancer cell growth signaling without affecting normal cells. Indeed, the administration of cytotoxic chemotherapeutic agents also induces apoptosis of normal cells (Guo et al., 2016).

The identification of protein-controlling cancer cell proliferation is promising for targeted protein-based cancer treatment development (An et al., 2021; Chang et al., 2022; Oshi et al., 2020). So far, MMP9 is widely discussed as the primary controller for cancer cell invasion, metastasis, and endothelial cell migration during angiogenesis (Jiang and Li, 2021; Joseph et al., 2020). Inflammatory microenvironment and hypoxia lead to the inactivation of p53, followed by activation of phosphatidyl inositol 3-kinase (PI3K) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), thereby accelerating cancer cell growth (Barillari, 2020; Luker et al., 2012). Adequate vascularization is required for tumors to grow and develop progressively through MMP9 signaling. Further evidence suggests that stromal-derived factor 1 (SDF1)/CXCR4 signaling also contributes to breast cancer cell survival and proliferation by promoting angiogenesis in the tumor area (He et al., 2018; Poltavets et al., 2021; Shi et al., 2020; Zhang et al., 2014). However, no study has confirmed the appearance of MMP9 and CXCR4 in breast cancer receiving neoadjuvant chemotherapy (NAC), so their prognostic value in breast cancer can be clearly understood.

As far as we know, this is the first study to highlight the value of angiogenesis inhibition by the NAC regimen. For these reasons, in this study, we investigated the MMP9 and CXCR4 expression shifting after NAC administration and so that part of the supporting pathway for reducing tumor size after NAC can be identified.

MATERIAL AND METHODS

Study design

This study retrospectively assessed basic clinical and demographic profiles, tumor features, therapeutic type (chemotherapy protocol and radical mastectomy), and follow-up data that was required from medical records. This study followed the principles of the Helsinki Declaration of 1975, and the protocol was approved by the ethics committee of Saiful Anwar Hospital (no.400/061/K.3/302/2021). All tissue samples were obtained from LABC, who received NAC for the first time.

Patients and tissue specimens

A total of 45 matched specimens of locally advanced breast cancer tissue, including 45 females (mean age, 52.5 ± 9.2 years), were obtained from each patient twice. First, breast cancer specimens were collected from patients who performed core needle biopsy (CNB) was called as before NAC treatment, and the second specimen was obtained from a surgical mastectomy resection procedure after NAC treatment at the Saiful Anwar General Hospital (East Java, Indonesia). All the samples enrolled in this study were histologically confirmed by pathologists, and patients who had received radiotherapy were excluded.

Tissue processing, embedding, and sectioning

In brief, 4 µm breast cancer (BC) tissue sections were deparaffinized with xylene and rehydrated through 100% ethanol. Heat-induced (pH6) citrate antigen retrieval was performed, and MMP9 and CXCR4 antibodies were incubated overnight at 4°C. 3-3′ diaminobenzidine tetrahydrochloride (Novolink

DAB substrate buffer plus) was used as the chromogen. Slides were counterstained with Novolink hematoxylin for 6 min, dehydrated, and cover slipped (Joseph et al., 2020).

MMP9 expression measurement

Both the percentage and staining intensity of MMP9 expression in LABC tissue were individually assessed, and the final histochemical score (H-score) was subsequently calculated (Joseph et al., 2020). MMP9 expression was confirmed with an anti-MMP9 antibody (ab38898) by immunohistochemical method. Interpretation of MMP9 was measured based on the intensity of staining. This intensity refers to a score of 0: none, 1: weak, 2: moderate, and 3: strong. If based on the percentage, 1: ≤25%, 2: 26-51%, 3: 51-75%, 4: ≥75%. The assessment is carried out by multiplying the intensity and percentage, where a score of 0-12 was obtained. Then, there were 2 groups of results: weak = 0-4 and strong 6-12 (Wu et al., 2021).

CXCR4 expression measurements

CXCR4 expression was confirmed with an anti-CXCR-4 antibody (ab1670) by immunohistochemical method. The CXCR4 score was interpreted based on immunoreactivity at 10 large visual fields (magnification 400×). Cell distributions were categorized as 0 = none, 1 = <10%, 2 = 10-50%, 3 = 51-80%, 4 = >80%. Intensity 0 = none, 1 = weak, 2 = moderate, 3 = strong. Histoscore (distribution × intensity); weak = 0-6, strong = 8-12 (Zhang et al., 2014).

Tumor mass evaluation

Tumor mass was defined as results of tumor size calculations before and after NAC administration using the formula V = (W2 × L)/2 for caliper measurements and the formula V = (4/3) × π × (L/2) × (L/2) × (D/2) for ultrasonography measurements, where V is tumor volume, W is tumor width, L is tumor length and D is tumor depth refers to tumor size calculation by Faustino-Rocha et al. (2013).

Statistical analysis

Statistical analysis between the two groups was calculated using Student's t-test. The correlation between MMP9 and CXCR4 expression level and clinicopathological data was analyzed using the Chi-square and Fisher exact test. Pre-post-test analyses were conducted to verify the disparity of cancer angiogenic markers before and after NAC administration. Data are shown as means ± standard deviation (SD) or standard error of the mean (SEM) from at least three independent experiments; $p<0.05$ was considered statistically significant. All statistical analyses were performed using Stata Statistical Software, version 15 (StataCorp LP, College Station, TX, USA).

RESULTS

On LABC, a variable degree of MMP9 and CXCR4 protein expression was observed (Figs. 1 and 2). Out of 45 informative H-scores, 93.3% showed low expression in cytoplasm, and 3.7% showed high expression. MMP9 was not associated with age at diagnosis, ER/PR status, HER2 status, Ki67 profile, and grading ($p>0.05$), likewise with CXCR4 expression (Table 1).

According to Table 1, this study discovered that LABC patients with a tumor expressing high MMP9 tended to show a negative HER2 appearance with high Ki67, while the number of LABC patients with a tumor expressing high CXCR4 tended to be dominant with positive ER/PR, HER2 positive, and high Ki67 characters, although overall not statistically significant. Corroborating with our results, the previous study reported that the general appearance of LABC is almost always associated with high cell proliferation rates as reflected by Ki67 and MMP9 expression, also associated with the high-risk of recurrence and poor survival (Cadona et al., 2017; Li et al., 2017; Soliman and Yussif, 2016; Zhang et al., 2014).

Patients with high CXCR4 also dominantly showed high Ki67 expression despite the correlation was not statistically significant. Previous research reported that high Ki67 is associated with large tumor size and higher pathologic state (Wei et al., 2018). This result showed that patients with low MMP9 expression had positive ER, HER2 positive, and high Ki76 characteristics, whereas patients with high CXCR4 had a clinical appearance of positive ER/PR, HER2 positive, and high Ki67. (Table 1).

There was no significant change in MMP9 expression ($p=0.500$) after the administration of NAC; instead, there was a significant change in the expression of CXCR4 after the administration of NAC ($p<0.001$). This shows that the administration of either anthracycline-based or taxane-based NAC has a pronounced effect on decreasing CXCR4 in locally advanced breast cancer tissue (Table 2). Neoadjuvant chemotherapy administration significantly reduced LABC tumor size ($p<0.001$) (Table 3). The intensity representation of MMP9 and CXCR4 expression in LABC tissue using the immunohistochemical was presented in Figs. 1 and 2.

Table 1. Association between MMP9 and CXCR4 protein expression and clinicopathological feature.

Parameters	MMP9 expression		p-value	CXCR4 expression		p-value
	Negative/low expression n (%) (n = 42)	High expression n (%) (n = 3)		Negative/low expression n (%) (n = 7)	High expression n (%) (n = 38)	
Age at diagnosis (years)	52.02 ± 1.4	59.67 ± 3.5	0.167[a]	53 ± 2.3	52.45 ± 1.6	0.886[a]
Estrogen (ER) status			0.548[b]			0.321[b]
Negative	8 (19.05)	0		0	8 (21.05)	
Positive	34 (80.95)	3 (100)		7 (100)	30 (78.95)	
Progesterone (PR) status			0.787[c]			0.633[c]
Negative	17 (40.48)	2 (66.67)		2 (28.57)	17 (44.74)	
Positive	25 (59.52)	1 (33.33)		5 (71.43)	21 (55.26)	
HER2 status			0.094[b]			0.366[c]
Negative	18 (42.86)	3 (100)		4 (57.14)	17 (44.74)	
Positive	24 (57.14)	0		3 (42.86)	21 (55.26)	
Ki67 status			0.595[b]			1.069[c]
Low	7 (16.67)	0		2 (28.57)	5 (13.16)	
High	35 (83.33)	3 (100)		5 (71.43)	33 (86.84)	
Grading			0.384[b]			0.105[b]
I	3 (7.14)	0		2 (28.57)	1 (2.63)	
II	20 (47.62)	3 (100)		3 (42.86)	20 (52.63)	
III	19 (45.24)	0		2 (28.57)	17 (44.74)	
Tumor mass (mean ± SD)	73.52 ± 5.54	119.50 ± 4.62	0.005	76.43 ± 16.36	76.62 ± 6.24	0.991[a]

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2. [a]t-test analysis; [b]Fisher exact test; [c] chi-square test.

Table 2. Anti-angiogenic effect of NAC based on MMP9 and CXCR4 expression in LABC.

Parameter	Neoadjuvant chemotherapy (n = 45)		p-value
	Pre NAC n (%)	Post NAC n (%)	
MMP9 expression			0.500
Weak	42 (93.3)	44 (97.8)	
High	3 (6.7)	1 (2.2)	
CXCR4 expression			<0.001
Weak	7 (15.6)	32 (71.1)	
High	38 (84.3)	13 (28.9)	

All data represent mean ± SD protein staining intensity.

Table 3. The anti-angiogenic effect of NAC reduced tumor mass in LABC.

Neoadjuvant chemotherapy	Tumor mass (mean ± SEM)	p-value
Pre	148.95 ± 23.4	**<0.000[a]**
Post	11.41 ± 1.8	

[a]P-value representation Paired T-test. NAC: neoadjuvant chemotherapy; SEM: standard error of the mean.

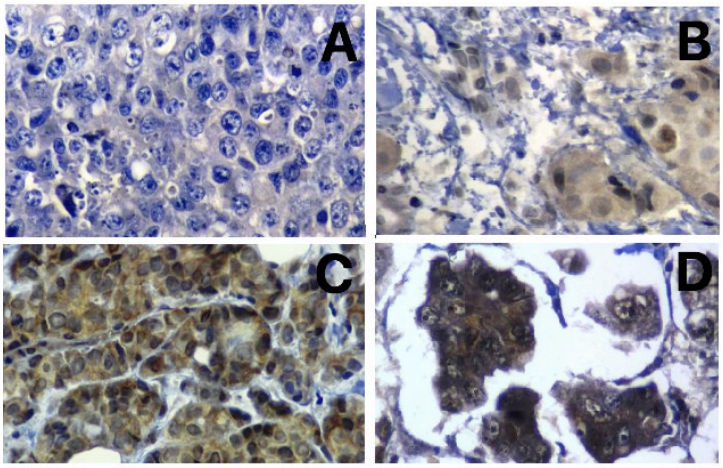

Figure 1. Immunohistochemical expression of CXCR4 in LABC.

(A) Negative stained, **(B)** low nuclear and cytoplasmic expression, **(C)** moderate nuclear and cytoplasmic expression, **(D)** high nuclear and cytoplasmic expression. All images are 400× magnification.

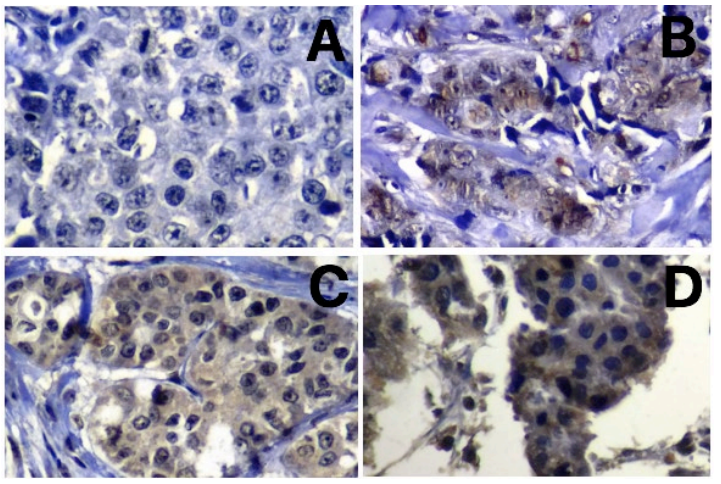

Figure 2. Immunohistochemical expression of MMP9 in LABC.

(A) Negative stained, **(B)** low nuclear and cytoplasmic expression, **(C)** moderate nuclear and cytoplasmic expression, **(D)** high nuclear and cytoplasmic expression. All images are 400× magnification.

DISCUSSION

The findings of this study suggest that a positive response to NAC with significantly reduced tumor size is supported by decreased expression of MMP9 and CXCR4 in LABC. CXCR4 possibly mediates LABC tumor size reduction. To the best of our understanding, this is the first study to confirm the anti-angiogenic effect (MMP9 and CXCR4 inhibitor) of anthracycline and taxane-based chemotherapy on LABC. It is well known that CXCR4 expression is increased in cancer cells (Ma et al., 2018; Zielińska and Katanaev, 2020), as well as reported in up to 50% of primary breast tumors, enhancing E2-mediated cellular growth (Al-Saleh et al., 2021; Bianchi and Mezzapelle, 2020; Xu et al., 2015). CXCR4 improves stem cell homing in tissue regeneration and significantly affects tumor size. Consequently, inhibition of CXCR4 activity is a priority target for cancer treatment (Xu et al., 2015). Reduction of CXCR4 expression after administration of NAC in this study indicates the anti-angiogenic effect of NAC on LABC, so these findings extend the understanding of pathways to inhibition of cancer cell proliferation.

Corroborating with our result, prior research reported that CXCR4 inhibitors, AMD3100 and TN14003, well organized, impair tumor growth and metastatic spread in vivo HER2 BC models but not in triple-negative (TN) BC (Lefort et al., 2017). Subsequently, another study found a tumor reduction rate of ≥60% was significantly associated with a reduced risk of recurrence and death (Angeles et al., 2019). Prior randomized and non-randomized trials also proved that women treated with neoadjuvant chemotherapy (NAC) and subsequent surgery had better disease-free survival (DFS) and overall survival (OS) (Cordoba et al., 2022).

Based on this statement, clinicians need to understand that reduced tumor size is an important determinant of patient outcome, and the development of potent CXCR4 and MMP9 inhibitors to encourage LABC tumor size reduction can be further investigated through ongoing research. Several angiogenesis inhibitors are clinically available for the treatment of various types of advanced solid cancer, such as small molecule tyrosine kinase inhibitors that target classic vascular endothelial growth factor (VEGF) and its

receptors (Ayoub et al., 2022). However, breast cancer is a persistent solid tumor that fails to respond to angiogenesis inhibitors. Our findings summarize current evidence regarding the effect of clinically available anti-angiogenic drugs in the treatment of breast cancer, which explains the evidence from studies targeting non-VEGF angiogenic pathways.

The results of this study prove that NAC mediates the decrease in MMP expression, although it is not statistically significant. Possibly, this is associated with MMP9 expression in LABC, which tends to be low in the group of participants who were observed and selected with non-metastatic criteria. Tumor vasculature disruption through controlling MMP9 activity is widely targeted in solid cancer therapy approaches, including breast cancer (Augoff et al., 2022; Winkler et al., 2020). Further research with a larger number of participants with high MMP9 expression is still needed to prove the anti-angiogenic effect of the NAC regimen.

CONCLUSION

The results underline that the angiogenic inhibitor of NAC, evidenced by the tendency to decrease MMP9 and CXCR4 expression, was associated with tumor mass reduction. However, the prognostic value of MMP9 CXCR4 in breast cancer still requires further functional investigations, mainly features of MMP9 and CXCR4 that elevate the risk of tumor recurrence.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

The authors thank the Pathology Anatomy division at Saiful Anwar General Hospital for tissue sample preparations and staining. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

ACS - The American Cancer Society Medical and Editorial Content Team (2021) Understanding a Breast Cancer Diagnosis. cancer.org. https://www.cancer.org/content/dam/CRC/PDF/Public/8580.00.pdf. [Accessed 12 June 2023].

Aebi S, Karlsson P, Wapnir IL (2022). Locally advanced breast cancer. Breast (Edinburgh, Scotland) 62: 58–62. https://doi.org/10.1016/j.breast.2021.12.011

Al-Saleh K, Salah T, Arafah M, Husain S, Al-Rikabi A, Abd El-Aziz N (2021) Prognostic significance of estrogen, progesterone, and HER2 receptors' status conversion following neoadjuvant chemotherapy in patients with locally advanced breast cancer: Results from a tertiary Cancer Center in Saudi Arabia. PLoS One 16: e0247802. https://doi.org/10.1371/journal.pone.0247802

Angeles MA, Baissas P, Leblanc E, Lusque A, Ferron G, Ducassou A (2019) Magnetic resonance imaging after external beam radiotherapy and concurrent chemotherapy for locally advanced cervical cancer helps to identify patients at risk of recurrence. Int J Gynecol Cancer 29: 480−486. https://doi.org/10.1136/ijgc-2018-000168

An J, Peng C, Tang H, Liu X, Peng F (2021) New advances in the research of resistance to neoadjuvant chemotherapy in breast cancer. Int J Mol Sci 22: 9644. https://doi.org/10.3390/ijms22179644

Augoff K, Hryniewicz-Jankowska A, Tabola R, Stach K (2022) MMP9: A tough target for targeted therapy for cancer. Cancers 14: 1847. https://doi.org/10.3390/cancers14071847

Ayoub NM, Jaradat SK, Al-Shami KM, Alkhalifa AE (2022) Targeting angiogenesis in breast cancer: Current evidence and future perspectives of novel anti-angiogenic approaches. Front Pharmacol 13: 838133. https://doi.org/10.3389/fphar.2022.838133

Balogun OD, Formenti SC (2015) Locally advanced breast cancer – strategies for developing nations. Front Oncol 5: 89. https://doi.org/10.3389/fonc.2015.00089

Barillari G (2020) The impact of matrix metalloproteinase-9 on the sequential steps of the metastatic process. Int J Mol Sci 21: 4526. https://doi.org/10.3390/ijms21124526

Bianchi ME, Mezzapelle R (2020) The chemokine receptor CXCR4 in cell proliferation and tissue regeneration. Front Immunol 11: 2109. https://doi.org/10.3389/fimmu.2020.02109

Cadona FC, Machado AK, Montano MAE, Assmann CE, da Cruz IBM (2017) Overview of locally advanced breast cancer: A huge challenge to science. Int J Womens Health Wellness 3: 044. http://doi.org/10.23937/2474-1353/1510044

Chang A, Sloan EK, Antoni MH, Knight JM, Telles R, Lutgendorf SK (2022) Biobehavioral pathways and cancer progression: Insights for improving well-being and cancer outcomes. Integr Cancer Ther 21: 15347354221096081. https://doi.org/10.1177/15347354221096081

Cordoba A, Durand B, Escande A, Taieb S, Amor MBH, Le Deley MC, Michel A, Le Tinier F, Hudry D, Martinez C, Leblanc E, Becourt S, Abdedaim C, Bresson L, Lartigau E, Mirabel X and Narducci F (2022) Prognostic impact of tumor size reduction assessed by magnetic resonance imaging after radiochemotherapy in patients with locally advanced cervical cancer. Front Oncol 12: 1046087. https://doi.org/10.3389/fonc.2022.1046087

Dhanushkodi M, Sridevi V, Shanta V, Rama R, Swaminathan R, Selvaluxmy G, Ganesan TS (2021) Locally Advanced Breast Cancer (LABC): Real-world outcome of patients from Cancer Institute, Chennai. JCO Glob Oncol 7: 767–781. https://doi.org/10.1200/GO.21.00001

Faustino-Rocha A, Oliveira PA, Pinho-Oliveira J, Teixeira-Guedes C, Soares-Maia R, da Costa RG, Colaço B, Pires MJ, Colaço J, Ferreira R, Ginja M (2013) Estimation of rat mammary tumor volume using caliper and ultrasonography measurements. Lab Animal 42: 217–224. https://doi.org/10.1038/laban.254

Gogia A, Deo SV, Shukla NK, Mathur S, Sharma DN, Tiwari A (2018) Clinicopathological profile of breast cancer: An institutional experience. Indian J Cancer 55: 210–213. https://doi.org/10.4103/ijc.IJC_73_18

Guo F, Wang Y, Liu J, Mok SC, Xue F, Zhang W (2016) CXCL12/CXCR4: A symbiotic bridge linking cancer cells and their stromal neighbors in oncogenic communication networks. Oncogene 35: 816–826. https://doi.org/10.1038/onc.2015.139

He W, Yang T, Gong XH, Qin RZ, Zhang XD, Liu, WD (2018) Targeting CXC motif chemokine receptor 4 inhibits the proliferation, migration, and angiogenesis of lung cancer cells.

Oncology Lett 16: 3976–3982. https://doi.org/10.3892/ol.2018.9076

Jiang H, Li H (2021) Prognostic values of tumoral MMP2 and MMP9 overexpression in breast cancer: A systematic review and meta-analysis. BMC Cancer 21: 149. https://doi.org/10.1186/s12885-021-07860-2

Joseph C, Alsaleem M, Orah N, Narasimha PL, Miligy IM, Kurozumi S, Ellis IO, Mongan NP, Green AR, Rakha EA (2020) Elevated MMP9 expression in breast cancer is a predictor of shorter patient survival. Breast Cancer Res Treat 182: 267–282. https://doi.org/10.1007/s10549-020-05670-x

Korde LA, Somerfield MR, Carey LA, Crews JR, Denduluri N, Hwang ES, Khan SA, Loibl S, Morris EA, Perez A, Regan MM, Spears PA, Sudheendra PK, Symmans WF, Yung RL, Harvey BE, Hershman DL (2021) Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO Guideline. J Clin Oncol 39: 1485–1505. https://doi.org/10.1200/JCO.20.03399

Larionova I, Kazakova E, Gerashchenko T, Kzhyshkowska J (2021) New angiogenic regulators produced by TAMs: Perspective for targeting tumor angiogenesis. Cancers 13: 3253. https://doi.org/10.3390/cancers13133253

Lefort S, Thuleau A, Kieffer Y, Sirven P, Bieche I, Marangoni E, Vincent-Salomon A, Mechta-Grigoriou F (2017) CXCR4 inhibitors could benefit to HER2 but not to triple-negative breast cancer patients. Oncogene 36: 1211–1222. https://doi.org/10.1038/onc.2016.284

Li H, Qiu Z, Li F, Wang C (2017) The relationship between MMP-2 and MMP-9 expression levels with breast cancer incidence and prognosis. Oncology Lett 14: 5865–5870. https://doi.org/10.3892/ol.2017.6924

Luker KE, Lewin SA, Mihalko LA, Schmidt BT, Winkler JS, Coggins NL, Thomas DG, Luker GD (2012) Scavenging of CXCL12 by CXCR7 promotes tumor growth and metastasis of CXCR4-positive breast cancer cells. Oncogene 31: 4750–4758. https://doi.org/10.1038/onc.2011.633

Ma J, Su H, Yu B, Guo T, Gong Z, Qi J, Zhao X, Du J (2018) CXCL12 gene silencing down-regulates metastatic potential via blockage of MAPK/PI3K/AP-1 signaling pathway in colon cancer. Clin Transl Oncol 20: 1035–1045. https://doi.org/10.1007/s12094-017-1821-0

Masood S (2016) Neoadjuvant chemotherapy in breast cancers. Womens Health 12: 480–491. https://doi.org/10.1177/1745505716677139

Oshi M, Takahashi H, Tokumaru Y, Yan L, Rashid OM, Nagahashi M, Matsuyama R, Endo I, Takabe K (2020) The E2F pathway score as a predictive biomarker of response to neoadjuvant therapy in ER+/HER2- breast cancer. Cells 9: 1643. https://doi.org/10.3390/cells9071643

Poltavets V, Faulkner JW, Dhatrak D, Whitfield RJ, McColl SR, Kochetkova M (2021) CXCR4-CCR7 heterodimerization is a driver of breast cancer progression. Life 11: 1049. https://doi.org/10.3390/life11101049

Shi Y, Riese DJ, Shen J (2020) The role of the CXCL12/CXCR4/CXCR7 chemokine axis in cancer. Front Pharmacol 11: 574667. https://doi.org/10.3389/fphar.2020.574667

Soliman NA, Yussif SM (2016) Ki-67 as a prognostic marker according to breast cancer molecular subtype. Cancer Biol Med 13: 496–504. https://doi.org/10.20892/j.issn.2095-3941.2016.0066

Wei DM, Chen WJ, Meng RM (2018) Augmented expression of Ki-67 is correlated with clinicopathological characteristics and prognosis for lung cancer patients: an up-dated systematic review and meta-analysis with 108 studies and 14,732 patients. Respir Res 19: 150. https://doi.org/10.1186/s12931-018-0843-7

Winkler J, Abisoye-Ogunniyan A, Metcalf KJ, Werb Z (2020). Concepts of extracellular matrix remodelling in tumour progression and metastasis. Nat Comm 11: 5120. https://doi.org/10.1038/s41467-020-18794-x

Wu HT, Lin J, Liu YE, Chen HF, Hsu KW, Lin SH, Peng KY, Lin KJ, Hsieh CC, & Chen DR (2021) Luteolin suppresses androgen receptor-positive triple-negative breast cancer cell proliferation and metastasis by epigenetic regulation of MMP9 expression via the AKT/mTOR signaling pathway. Phytomedicine 81: 153437. https://doi.org/10.1016/j.phymed.2020.153437

Xu C, Zhao H, Chen H, Yao Q (2015) CXCR4 in breast cancer: oncogenic role and therapeutic targeting. Drug Des Devel Ther 9: 4953–4964. https://doi.org/10.2147/DDDT.S84932

Zielińska KA, Katanaev VL (2020) The signaling duo CXCL12 and CXCR4: Chemokine fuel for breast cancer tumorigenesis. Cancers 12: 3071. https://doi.org/10.3390/cancers12103071

Zhang Z, Ni C, Chen W, Wu P, Wang Z, Yin J, Huang J, Qu F (2014) Expression of CXCR4 and breast cancer prognosis: a systematic review and meta-analysis. BMC Cancer 14: 49. https://doi.org/10.1186/1471-2407-14-49

AUTHOR CONTRIBUTION:

Contribution	Budianto M	Lubis H	Fadli M	Nurwidyaningtyas W
Concepts or ideas	x	x		
Design	x	x		x
Definition of intellectual content	x	x	x	x
Literature search		x		x
Experimental studies	x	x		
Clinical trial		x	x	
Data acquisition	x		x	x
Data analysis		x		x
Statistical analysis				x
Manuscript preparation	x	x		x
Manuscript editing	x	x		x
Manuscript review	x	x	x	x

Citation Format: Budianto M, Lubis H, Fadli M, Nurwidyaningtyas W (2023) Check update pattern of tumorigenic vasculature signature based on MMP9 and CXCR4 expression in locally advanced breast cancer. J Pharm Pharmacogn Res 11(6): 926–933.
https://doi.org/10.56499/jppres23.1695_11.6.926