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LITERATURE REVIEW

ANALYSIS OF THE EFFECTIVENESS OF DUAL PI3K/mTOR INHIBITORS IN INHIBITION OF PI3K/AKT/mTOR SIGNALING PATHWAY IN BREAST CANCER

(ANALISIS EFEKTIFITAS DUAL PI3K/mTOR INHIBITOR DALAM PENGHAMBATAN PI3K/AKT/mTOR SIGNALING PATHWAY PADA KANKER PAYUDARA)

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ABSTRACT

Breast cancer is a malignancy originating from breast cells, ducts, and tissues that can occur due to genetic mutations due to DNA damage in normal cells. The PI3K/Akt/mTOR pathway is an intracellular pathway that plays an important role in regulating basic cell functions such as cell growth, movement, survival, metabolism, and angiogenesis. Some examples of PI3K/mTOR pathway inhibitor drugs on the market and often used are *dactolisib, samotolisib, voxtalisib*, and so on. These drugs are more effective than single-pathway inhibitors. This article was prepared using the literature review method. The data used in this article were obtained from the *PubMed* and *Google Scholar* using the keywords breast cancer, PI3K/Akt/mTOR inhibitor, and PI3K/AKT/mTOR signaling pathway. Several studies suggest that the PI3K-AKT-mTOR pathway is critical in mediating the proliferation and migration of breast cancer cells. Because of the importance of the PI3K-AKT-mTOR pathway in the pathogenesis of breast cancer, it is often used as a target for breast cancer therapy. PI3K/mTOR dual ATP competitive inhibitors can directly act on the main target proteins of PI3K and mTOR, thereby more efficiently inhibiting the PI3K/AKT/mTOR signaling pathway and effectively preventing other factors that can activate the PI3K pathway, and reducing the resistance and side effects produced by single inhibitors.

Keywords: breast cancer, dual inhibitor, PI3K-AKT-mTOR

ABSTRAK
Kanker payudara merupakan keganasan yang berasal dari sel epitel kelenjar payudara yang dapat terjadi karena adanya mutasi genetik akibat kerusakan DNA pada sel normal. Jalur PI3K/Akt/mTOR merupakan jalur intraseluler yang berperan penting dalam mengatur fungsi dasar sel seperti pertumbuhan, pergerakan, kelangsungan hidup, metabolisme, dan angiogenesis sel. Beberapa contoh obat penghambat jalur PI3K/mTOR yang beredar di pasaran dan sering digunakan yaitu dactolisib, samotolisib, voxtalisib, dan sebagainya. Obat-obatan ini lebih efektif dibandingkan penghambat jalur tunggal. Artikel ini disusun menggunakan metode telaah pustaka, data yang digunakan pada artikel ini diperoleh dari search engine PubMed dan Google Scholar dengan menggunakan kata kunci breast cancer, PI3K/Akt/mTOR inhibitor, dan PI3K/AKT/mTOR signaling pathway. Beberapa studi mengemukakan bahwa, jalur PI3K-AKT-mTOR sangat penting dalam memediasi proliferasi dan migrasi sel kanker payudara. Jalur PI3K-AKT-mTOR mempunyai peranan penting di patogenesis kanker payudara sehingga sering dijadikan target terapi kanker payudara. PI3K/mTOR dual ATP competitive inhibitors dapat langsung bekerja pada protein target utama PI3K dan mTOR, sehingga lebih efisien menghambat jalur pensinyalan PI3K/AKT/mTOR, dan secara efektif mencegah faktor-faktor lain yang dapat mengaktifkan jalur PI3K, serta mengurangi resistensi dan efek samping yang dihasilkan oleh inhibitor tunggal.

Kata Kunci : dual inhibitor, kanker payudara, PI3K-AKT-mTOR

INTRODUCTION

Breast cancer is a malignancy originating from the epithelial cells of the glandular acini, ductuli or ductus mammae, and fibroglandular tissue of the breast, which may occur due to genetic mutations resulting from DNA damage in normal cells.[1] Breast cancer is one of the most common types of cancer among women worldwide, including Indonesia.[2,3] The exact cause of breast cancer remains unknown; however, several risk factor may trigger its occurrence, including a family history of breast cancer, age over 50 years, being overweight, alcohol consumption, smoking, long-term use of hormonal contraceptives, radiation exposure, late menopause, and early menarche. [4]

According to data from the International Agency for Research on Cancer (2022), breast cancer ranks second among the 15 most common cancer worldwide, with more than 2 million reported cases. Meanwhile, based on data from GLOBOCAN (Global Cancer Observatory) in 2022, breast cancer ranks first in Indonesia, with more than 60,000 reported cases.[5] In the United States, approximately 40,000 women have died from breast cancer in recent decades, prompting the development of several therapeutic methods to inhibit the PI3K/Akt/mTOR pathway.[6]

Excessive activity of the PI3K/Akt/mTOR pathway can trigger neoplasms by regulating cell growth,

motility, survival, metabolism, and angiogenesis in cancer cells, as well as inhibiting apoptosis through the suppression of the p53 gene, caspase 3, Fas receptor (CD59), and TNF receptor (TNFR1).[7,8] several PI3K/mTOR pathway inhibitors, such as dactolisib, samotolisib, and voxtalisib, have shown greater effectiveness compared to single-pathway inhibitors. This literature review aims to analyze the effectiveness or outcomes of dual PI3K/mTOR inhibitors as a therapeutic target in breast cancer.

METHODS

The method used in this article is a literature review, with literature searches conducted through PubMed and Google Scholar. The keywords used were "*breast cancer"*, "*PI3K/Akt/mTOR inhibitor",* and "*PI3K/Akt/mTOR signaling pathway"*. The inclusion criteria were articles published within the last 10 years, full-text articles accessible in English

The next stages included articles, developing a matrix to compare research findings, selecting relevant articles, and conducting an in-depth analysis.

RESULT AND DISCUSSION

This literature search identified four articles that met the eligibility criteria for inclusion in this review. The extracted findings are summarized in Table 1.

Table 1 Results of literature search on dual PI3K/mTOR inhibitors as therapeutic targets in breast cancer

Author (Year)	Objective	Findings
Li *et al*. (2022)[8]	This article comprehensively explains the genetic alterations in normal individuals and those with tumors, and discusses the role of targeted inhibitors in cancer therapy, particularly the role of the PI3K/AKT/mTOR signaling pathway and RAF/MEK/ERK in supporting tumor growth.	Both the PI3K/AKT/mTOR and RAF/MEK/ERK pathways are often involved in breast cancer therapy. Similarly, dual PI3K/mTOR inhibitors may represent a potential antitumor approach compared to PI3K or mTOR inhibitors alone
Mezni *et al.* (2020)[9]	This article reviews recent therapeutic developments and the latest achievements in the field. These new agents may act at several levels and have different targets and mediators. Schematically, this study distinguishes pertuzumab, lapatinib, and adotrastuzumab emtansine (T-DM1) based on their interactions with the HER2 molecule	Therapeutic recommendations for HER2-positive metastatic breast cancer (MBC) represent a dynamic and innovative field with the emergence of new therapies. Several novel agents, such as DS-8201 and tucatinib, have demonstrated promising effectiveness. In addition to evaluating new drugs, combinations that integrate multiple mechanisms of action-including chemotherapy, cell cycle inhibitors, immunotherapy, and

Author (Year)	Objective	Findings
		PI3K/mTOR inhibitors should be further explored
Luo *et al.* (2023)[7]	The objective of this study was to explore the effects of XIN-10, a dual PI3K/mTOR inhibitor, on tumor growth and anti-proliferation, as well as to further investigate the antitumor mechanisms of XIN-10	A series of in vitro and in vivo experiments demonstrated that XIN-10 exhibits superior anti-proliferative activity compared to the reference drug GDC-0941. Furthermore, based on protein blotting and PCR experiments, the authors concluded that XIN-10 can inhibit activations of the mTOR pathway by suppressing AKT (S437) phosphorylation and exerts a significant inhibitory effect on PI3K and mTOR gene exons.
Park *et al.* (2020)[10]	This study treated breast cancer cells, MCF-7 and MDA-MB-231, with conditioned media derived from mesenchymal adipocytes of mouse 3T3-L1 cells or adipocytes derived from mesenchymal stem cells of human adipose tissue (hAMSCs). Cell viability and proliferation were then analyzed using the MTT assay. In addition, mRNA expression of inflammatory cytokines and protein expression in key signaling pathways were analyzed using RT-qPCR and immunoblotting, respectively.	Conditioned media derived from adipocytes enhanced the proliferation and migration of breast cancer cells through the PI3K/AKT/mTOR pathway, underscoring the importance of heterotypic interactions between breast cancer cells and adiposity within the tumor microenvironment.

Breast Cancer

The incidence and mortality rates of breast cancer have tended to increase over the past three decades due to several risk factors and the lack of early detection.[2] Breast cancer may metastasize to various organs such as the bone, liver, lung, and brain. It typically originates from epithelial cells in the ductolobular system of the breast, which subsequently develop into cancer and may spread to other organs. Tumor microenvironment, such as stromal cells or macrophages, play an important role in the initiation and progression of breast cancer.[11]

Several hallmarks of cancer play an important role in the development of breast cancer including sustaining proliferative signaling, evading growth suppressors, avoiding immune destruction, and enabling replicative immortality, among others. More recently identified hallmarks include unlocking phenotypic plasticity, non-mutational epigenetic reprogramming, polymorphic microbiomes, and senescent cells.[12]

Early detection methods to prevent breast cancer include breast self-examination (BSE).[13] Other screening methods that can be performed are mammography and breast magnetic resonance imaging (MRI). The advantage of breast cancer screening is the ability to detect or diagnose breast cancer at an early stage, allowing earlier treatment to reduce mortality rates. However, there are also certain risks associated with breast screening, such as false-positive results, which may lead to overdiagnosis and overtreatment.[14]

PI3K/AKT/mTOR *Signaling Pathway*

The PI3K/AKT/mTOR pathway is a major signal transduction network in all eukaryotic cells, playing a role in regulating cell survival, growth, and proliferation in response to external stimuli. The two main functional proteins in this pathway are PI3K and AKT. Mutations in several components of this pathway have been associated with human oncogenesis. Therefore, activation of membrane receptors (RTK or GPCR), induction of the PI3K oncogene, amplification of kinases such as PI3KCA, and decreased PTEN expression can contribute to cancer development. Excessive activity of the PI3K/AKT/mTOR pathway may also trigger epithelial-mesenchymal transition (EMT) and metastasis.[15]

mTOR interacts with other proteins and constitutes a component of two protein complexes, mTORC1 and mTORC2, which regulate various cellular activities. mTORC1 is triggered by different nutrients and can be stimulated by PI3K signaling. mTORC1 functions as an upstream regulator, while mTORC2 acts as a downstream effector of AKT. AKT is an essential substrate of mTORC2 and has been shown to play an active role in malignancy. AKT integrates signal from PI3K/mTORC2 and PI3K/PDK1 to promote cell survival, growth, and proliferation. Small molecules such as hormones and growth factors can activate AKT, mTORC2, and subsequently mTORC1 through AKT-dependent phosphorylation pathways. Nutrients, on the other hand, can activate AKT and mTORC2, and directly stimulate mTORC1 through AKT-independent phosphorylation pathways.[16] mTOR then promotes the binding of cyclin D1 to cyclin-dependent kinase (CDK) to initiate cell division. Overexpression of cyclin D1 can induce the transition of the cell cycle from the G1 to the S phase, shorten the cell cycle, and accelerate cancer progression.[17]

PI3K Inhibitor* dan *Dual PI3K/mTOR Inhibitors

The first generation of PI3K inhibitors, Wortmannin and LY294002, are capable of binding to all class I PI3K and

are therefore referred to as "*pan-inhibitor*".[18] These compounds have been widely used in preclinical studies but exhibit poor pharmacokinetics, which prevented their development as anticancer drugs. In recent years, compounds with improved pharmacokinetic properties have been developed and are currently undergoing clinical trials.[19] These second-generation inhibitors are characterized by greater and more specific selective activity. Third-generation compounds, known as dual PI3K/mTOR inhibitors, were developed in consideration of the structural similarities in the catalytic sites of PI3K and mTOR. The potential advantage of these new compounds is that they not only inhibit all class I PI3K isoforms but also suppress both mTORC1 and mTORC2 .[20]

One of the limitations of chemotherapy drugs is chemoresistance. Activation of the PI3K/AKT/mTOR pathway in cancer promotes rapid cancer cell proliferation. Therefore, the development of small molecules targeting the PI3K/AKT/mTOR signaling pathway is expected to inhibit its activity, suppress cell proliferation, and enhance sensitivity to chemotherapy drugs. There is regulatory interplay among PI3K, AKT, and mTOR; for example, when mTORC1 is inhibited, PI3K and AKT may be reactivated through feedback mechanisms, thereby reducing the effectiveness of single-target small-molecule inhibitors of the mTOR pathway. Dual PI3K/mTOR inhibitors are being developed to simultaneously target the kinase sites of PI3K, mTORC1, and mTORC2. Inhibition of PI3K proteins can prevent the binding of the p110 and p85 subunits, thereby blocking the conversion of the phosphatidylinositol 3,4-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3). As a result, PIP3 is unable to bind to phosphoinositide-dependent kinase-1 (PDK1), which is required for AKT phosphorylation. AKT is a signal transduction protein capable of phosphorylating several substrates such as mTOR, MMP, and CDK, which play critical roles in triggering anti-apoptosis, angiogenesis, and metastasis.[21]

Dual PI3K/mTOR *inhibitors* that have entered clinical evaluation have not yet achieved optimal outcomes due to frequent toxicity. This occurs because dual PI3K/mTOR inhibitors target multiple proteins that play fundamental roles in various normal tissues. The main toxicities include diarrhea, vomiting, nausea, rash, fatigue, loss of appetite, hyperglycemia, mucositis, elevated liver enzymes, and thrombocytopenia. Different dosing schedules may improve the toxicity profile and provide the best therapeutic window.[22] In addition, severe adverse effects include hyperglycemia, hyperlipidemia, bone marrow suppression, and pneumonitis.

Therefore, a through understanding of the molecular basis of these side effects is necessary to aid in the development of optimal preventive and therapeutic strategies.[23]

The PI3K/AKT/mTOR signaling pathway is a signaling cascade that plays an important role in the process of cancer development in humans. PI3K promotes the transfer of PIP2 to PIP3 through phosphatidylinositol phosphorylation. PIP3 serves as the basis for several downstream targets of the PI3K/AKT/mTOR pathway. PI3K consists of three classes, class I, II, and III distinguished by their structure, reaction mechanisms, and characteristics. The N-terminal region of AKT, which anchors to PI (3,4,5) P3, contributes to its translocation to the cytomembrane, leading to AKT activation through phosphorylation at two amino acid residues. AKT includes phosphorylation of PRAS40 and the tuberous sclerosis complex (TSC2) to reduce their inhibitory effects on mTORC1, thereby including mTOR activation. mTORC2 is another mTOR complex besides mTORC1. mTOR is a type of protein kinase within the PI3K-related kinase family. The regulator/Rag GTPase complex acts as a regulator in controlling mTORC1 activity. AKT is a key node that transduces signals from mTORC2 to mTORC1, while mTORC1 can also be regulated independently of mTORC2.[7, 8]

PI3K/mTOR dual inhibitors demonstrate strong activity against all p110 isoforms and mTOR, combining multiple therapeutic effects within a single molecule. Compared with other types of PI3K pathway inhibitors, PI3K/mTOR dual inhibitors target all catalytic forms of PI3K, mTORC1, and mTORC2, and can effectively overcome the feedback inhibition observed when mTORC1 inhibitors are used alone. PI3K/mTOR dual inhibitors are more effective that agents that target only a single protein.[24]

The dual PI3K/mTOR inhibitor XIN-10 has been reported to effectively inhibit the growth of MCF-7 cells. In quantitative fluorescence PCR experiments, XIN-10 significantly suppressed the expression of PI3K and mTOR genes in MCF-7 cells which are known to drive cancer progression. TUNEL (TdT-mediated dUTP Nick End Labeling) staining and immunohistochemical assays on transplanted tumors demonstrated that XIN-10 induced apoptosis in MCF-7 xenograft tumors. PCR results confirmed that this compound markedly inhibited the expression of PI3K and mTOR, suggesting that it may serve as a promising therapeutic approach for breast cancer treatment. Single mTOR inhibitors often trigger negative feedback regulation of AKT, thereby reactivating the PI3K pathway. Selective PI3K inhibitors are frequently affected by

mutations in the p110α catalytic subunit, leading to drug resistance, although they can avoid the negative feedback regulation of AKT. PI3K monotherapy also interferes with insulin metabolism, causing side effects such as hyperglycemia, anorexia, and nausea. Dual ATP-competitive PI3K/mTOR inhibitors directly target both PI3K and mTOR, making them more efficient in suppressing the PI3K/AKT/mTOR signaling pathway. They can also effectively prevent other factors from reactivating the PI3K pathway, thereby reducing resistance and minimizing the side effects associated with single inhibitors. Currently, several examples of dual PI3K/mTOR inhibitors such as Gedatolisib, Omipalisib, and Apitolisib are under investigation in phase I and II clinical trials.[7]

Studies on PI3K/mTOR dual inhibitors have shown that several molecular mechanisms influence their antitumor activity. Within the PI3K/mTOR signaling pathway, mutation in the PI3KCA gene, which encodes PI3Kα, and loss of phosphatase and tensin homolog (PTEN) can increase sensitivity to PI3K/mTOR dual inhibitors. Various biological processes, including compensatory signaling pathways, epithelial-mesenchymal transition, and drug efflux via ATP-binding cassette transporters, can mediate cellular resistance to PI3K/mTOR dual inhibitors. Identifying the molecular determinants that affect the antitumor activity of these inhibitors is essential to maximize clinical outcomes in PI3K/mTOR dual inhibitor therapy.[25]

Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu) are important biomarkers in breast cancer. Standard pathological assessments can determine clinically useful subgroups based on the status of these three biomarkers, such as triple-negative, hormone receptor-positive, and HER2-positive breast cancer. Therapeutic strategies for breast cancer over the past few decades have led to improved survival rates in patients. However, breast cancer remains a leading cause of cancer-related mortality, largely due to drug resistance, recurrence, and severe side effects. Recent studies highlight that the tumor microenvironment (TME), particularly adipocyte-derived cells, plays an important role in the progression of various human cancers, including breast cancer. In addition to adipocytes in the TME, the PI3K-AKT-mTOR pathway is also crucial in meditating the proliferation and migration of breast cancer cells. This pathway plays a central role in the pathogenesis of breast cancer and is therefore frequently targeted in therapy. P13K/AKT/mTOR inhibitors are classified into four categories: PI3K inhibitors, AKT

inhibitors, mTOR inhibitors, and PI3K/mTOR dual inhibitors. The most well-known mTOR inhibitor is rapamycin, which binds directly to the active domain of the kinase. Classic PIEK inhibitors include wortmannin and LY294002, which suppress cell proliferation and induce apoptosis in in vitro and animal models. The development of dual inhibitors targeting both PI3K and mTOR has been extensively investigated. BEZ235 is dual PI3K/mTOR inhibitor with therapeutic potential in breast cancer by inducing cell cycle arrest and apoptosis.[10]

Therapeutic combinations that integrate multiple mechanisms of action including chemotherapy, cell cycle inhibitors, immunotherapy, and PI3K/mTOR inhibitors require further investigation. The clinical application of such strategies will necessitate the development and integration of biomarkers capable of identifying subgroups most likely to benefit from specific novel agents and therapeutic combination.[9]

CONCLUSION

PI3K/mTOR dual inhibitors exhibit strong activity against cancer cells and can effectively suppress tumor growth. The use of single inhibitors is often limited by drug resistance and significant side effects, whereas PI3K/mTOR dual inhibitors are more efficient in overcoming these challenges. Identifying molecular factors that influence the antitumor activity of PI3K/mTOR dual inhibitors is essential to maximize clinical outcomes. Biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu) play a crucial role in guiding breast cancer treatment strategies. The tumor microenvironment (TME) also contributes significantly to breast cancer progression, while the PI3K-AKT-mTOR pathway is critical in mediating cell proliferation and migration. Therapeutic combinations that integrate multiple mechanisms of action, including PI3K/mTOR inhibition, warrant further investigation to enhance cancer treatment efficacy, and the development of appropriate biomarkers will be necessary to identify patient subgroups most likely to benefit from such therapies.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with any parties related to this literature review.

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