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PI3K/AKT/mTOR Inhibitor Drug Candidates for the Treatment of Hormone Resistant Breast Cancer: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

Breast cancer is the second most diagnosed type of cancer in women, with approximately 2.3 million cases reported in 2020. According to estimates by Brazil's National Cancer Institute, there will be approximately 74,000 new cases in the three-year period 2023-2025. It is divided into 4 molecular subtypes, Luminal A, Luminal B (hormone-positive), HER-2 and triple-negative. Regarding treatment, particularly for the luminal subtypes, hormone therapy is fundamental, since they grow from estrogen stimulation. However, processes can occur that lead to therapeutic

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resistance, such as mutations in the PI3K/AKT/mTOR pathway, which acts in the regulation of various cellular functions. The search for drugs that inhibit this pathway as an alternative treatment may play a key role in overcoming this resistance. This systematic review aimed to study new candidate drugs for inhibiting the PI3K/AKT/mTOR pathway as an alternative treatment in cases of resistance to hormone therapy. The study was conducted in accordance with the PRISMA guidelines, using the PubMed database with the following terms: "breast cancer", "PI3K/AKT/mTOR", "immunotherapy" without restriction of year and language. A total of 36 articles were found and 3 were included in this review. The drug candidates presented promising results in terms of inhibiting the PI3K/AKT/mTOR pathway, as well as some advantages such as a reduction in adverse effects, an increase in the average density of cytotoxic T cells and greater expression of interferon signaling genes, which through their immunoregulatory function lead to an increase in the body's ability to react to tumor cells. Despite this, there is still a need for more studies on the subject, especially in vivo studies that can assess the biosafety and efficacy profile, with the aim of compiling sufficient data to make the introduction of these new drugs in breast cancer therapy a reality.

Keywords: Breast cancer; PI3K/AKT/mTOR; luminal; immunotherapy; tumor cells; cancer therapy; skin cancer; non-melanoma.

1. INTRODUCTION

Breast cancer is the second most diagnosed type of cancer in women, second only to non-melanoma skin cancer, with approximately 2.3 million new cases reported in 2020, representing 24.5% of new cases in women, making it the most frequent cause of death in these patients, with 684,996 deaths in the same year [1]. In Brazil, rates are higher in regions with a higher development index, such as the South and Southeast. Some data estimate that in the three-year period 2023-2025 there will be approximately 704,000 new cases of cancer, of which 74,000 will be breast cancer, corresponding to 10.5% of all cancer cases [2].

The clinical, morphological and biological complexity of breast cancer means that breast tumors have different prognoses and responses. In view of this, there is a need for these tumors to be classified according to markers identified by immunohistochemistry (IHC), such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth receptor 2 (HER2) and cell proliferation index (Ki-67), in addition to tumor size, tumor grade and lymph node status [3]. Thus, breast cancer can be classified into different molecular subtypes, the luminal A, luminal B, HER2 and triple negative subtypes [4].

Luminal A is defined as ER positive, PR>20%, HER2 negative and Ki67<14%. Tumors of the luminal B subtype are positive for at least one of the hormone receptors (ER and PR), but expressed to a lesser extent compared to luminal A, can be HER2 positive or negative and have a Ki-67 index equal to or greater than 14%. In the HER2 subtype, there is an absence of both estrogen and progesterone receptors, only HER2 positivity. Finally, the triple-negative molecular subtype is one that is negative for both estrogen, progesterone and HER2 receptors, usually associated with high Ki-67 values [5].

Molecular subtypes are important both for diagnosis and for directing treatment, which includes surgery, radiotherapy and systemic therapy [6,7]. Systemic therapy for breast cancer comprises hormone therapy, chemotherapy, molecular target therapy and immunotherapy [8].

In the Luminal A and Luminal B subtypes, hormone therapy is indispensable. Today there are different options, but all with the same objective, which is to prevent the interaction of estrogens and modulate dependent pathways. However, approximately 50% of hormone-positive breast cancers end up acquiring resistance to hormone therapy, and this occurs through various mechanisms such as somatic changes, epigenetic changes and changes related to the tumor microenvironment [9].

The PI3K/AKT/mTOR pathway regulates various normal cell functions such as cell proliferation, growth, survival and cell motility. Occasionally, mutations occur in this pathway, which generates an abnormality in various types of tumors and can lead to resistance to treatment in cases of breast cancer, including hormone-positive cancers [10]. To overcome this problem, Alpelisib, a drug that selectively inhibits the alpha isoform of PI3K, is used to treat HR+ metastatic

breast cancer. However, the use of this drug can lead to adverse effects that impair therapeutic adherence, such as hyperglycemia. In the SOLAR-1 study, 63.7% of patients treated with Alpelisib had hyperglycemia of any degree and 36.6% had grade 3-4 hyperglycemia. This leads to treatment discontinuation, as it is a disadvantage of using this inhibitor, justifying the study of new inhibitors that minimize the adverse effects that impair therapeutic adherence [11].

Therefore, the aim of this study was to carry out a systematic review of the literature on new candidate drugs for inhibiting the PI3K/AKT/mTOR pathway as an alternative treatment in cases of resistance to hormone therapy in breast cancer patients.

2. METHODOLOGY

The review was conducted according to the PRISMA guidelines, which consist of a four-phase flow diagram and a 27-item checklist. Compliance with the items on the list reflects on clarity, transparency of results and consistent analysis [12].

2.1 Study Selection

Initially, a literature search was carried out using the database PubMed database, using the following descriptors: "breast cancer", "PI3K/AKT/mTOR" and "immunotherapy" with no restrictions on year or language.

2.2 Inclusion Criteria

Only original articles analyzing inhibitors of the PI3K/AKT/mTOR pathway for the treatment of hormone receptor-positive breast cancer were selected.

2.3 Exclusion Criteria

The following types of study will be discarded: studies on non-luminal subtypes, proceedings of events, bibliographical reviews, book chapters, studies on resistance to trastuzumab, studies on the action of specific receptors, studies on other types of cancer.

2.4 Inclusion of Studies

It was carried out in accordance with the eligibility criteria, according to two independent reviewers.

2.5 Data Extraction

The data was extracted independently, in duplicate, to ensure consistency. The following information was collected: title, objective, sample/population studied and results.

3. RESULTS AND DISCUSSION

A total of 36 studies were found by searching the PubMed database. After review, a total of 33 articles were excluded and the remaining 3 articles were included in the review. A summary of the selection process according to the PRISMA guidelines is presented in Fig. 1 and an overall summary of data collection is presented in Table 1.

BCSCs breast cancer stem cells; HNK Honokiol; PTTH identified potential therapeutic targets of honokiol; mBCSC metastatic BCSC cell cycle arrest; PI3K phosphatidyl-inositol 3-kinase; AKT protein kinase B; mTOR mammalian target protein of rapamycin.

Hormone therapy is essential for all breast cancer patients with positive hormone receptors. Its aim is to prevent the interaction between estrogen and dependent pathways that stimulate the growth and proliferation of neoplastic cells. The main mechanisms by which the therapy works are blocking estrogen production and blocking estrogen action against tumor cells [9]. Aromatase inhibitors such as letrozole, anastrazole, exemestane, selective ER modulators such as tamoxifen and ER down-regulators such as fulvestrant are among the most widely used therapeutic choices in hormone-positive tumors [13].

Resistance to endocrine therapy can be divided into intrinsic (de novo) or acquired. Approximately 50% of patients with hormone-positive breast cancer have acquired resistance to hormone therapy, 25% of them in the early stages of the disease. In cases of metastasis, almost all patients develop some form of resistance, leading to complications in the clinical outcome [14].

One of the factors leading to resistance is the activation of the mTOR cellular pathway where its substrate s6 kinase beta-1, phosphorylates the estrogen ligand-independent activator domain [9]. In addition, hormone resistance can be associated with ligand-independent ER reactivation due to mutations and/or gain of

function in the receptor, altered interactions with coactivators, or through compensatory cross-interaction between ER and growth factor receptors, as well as oncogenic signaling pathways [15].

Through molecular analysis and large-scale DNA sequencing in relation to ER, it has been noted that breast tumors can undergo somatic changes related to poor response to hormone therapy in long-term treatment, making them resistant to previously used drugs [15].

Considering the relevance of the PI3K/AKT/mTOR pathway to cell growth, survival and proliferation, genetic alterations found in this pathway are often expected. These alterations promote hyperactivation of this pathway, which consequently leads to cancer cell proliferation, cell transformation and resistance to apoptosis. To circumvent the survival of estrogen-independent cancer cells, the combined inhibition of ER and PI3K has synergistic effects [13].

Pre-clinical studies have elucidated that activation of the mTOR pathway functions as a mechanism of acquired resistance to long-term estrogen deprivation, which has led to further research being carried out to explore this pathway as a mechanism to prevent estrogen-independent cell survival [13].

In this review, the study by Skolastika et al [16] analyzed the molecular mechanisms underlying cell cycle arrest mediated by HNK, a bioactive polyphenol isolated from the bark and seed pods of *Magnolia spp*, as well as its impacts on the immune environment. Through bioinformatics analysis, this study identified the potential targets and molecular mechanisms of the HNK molecule in the cell cycle with the help of data from metastatic breast cancer cells obtained from the GEO database. It was observed that HNK has anticancer effects by suppressing angiogenesis, migration, invasion and proliferation in a variety of cancer cell lines and tumor models. In addition, the results showed that the therapeutic targets of HNK can modulate the PI3K/AKT/mTOR and HIF1/NFkB pathways through their inhibition, which makes the molecule a potential agent capable of overcoming hormonal resistance in breast cancer cells by modulating the tumor environment [16]. Despite this, the researchers found that the molecular mechanisms underlying the effects of the Honokiol molecule on the metastatic axis of the cell cycle have not been elucidated. Another limitation observed was that the HNK targets were predicted from databases, and that using a bioinformatics approach makes it necessary to carry out further in vitro and in vivo tests [16].

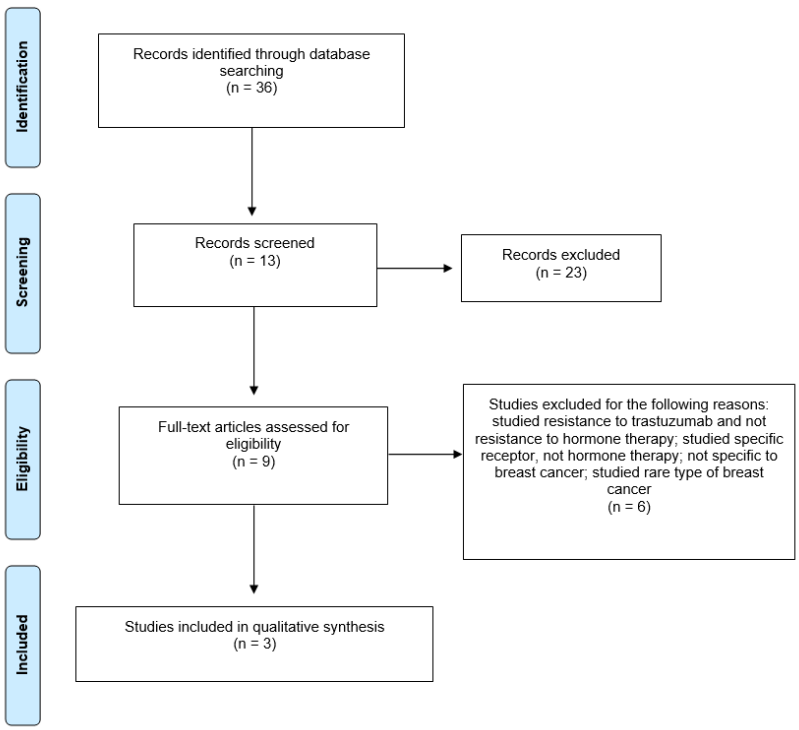

Fig. 1. PRISMA flowchart for the selection of studies

Table 1. Description of the main data from the included studies

Title	Aim	Sample/Study population	Results
Comprehensive Computational Analysis of Honokiol Targets for Cell Cycle Inhibition and Immunotherapy in Metastatic Breast Cancer Stem Cells	To explore the molecular mechanisms subjacent HNK-mediated mBCSC cell cycle arrest, as well as to evaluate the impact of this compound on the immune environment using bioinformatics studies.	Metastatic breast cancer stem cell data was collected from the GEO database (https:/www.ncbinim.nih govigeo) using keywords such as metastatic breast cancer stem cells and *Homo sapiens.*	Interaction between HNK and two HNK targets that regulate the cell cycle was analyzed using molecular docking analysis. Potential therapeutic targets were identified, which can inhibit the cell cycle of mBCSCs. In addition, the results showed that PTTH can modulate the PI3K/Akt/mTOR and HIF 1/NF F pathways. These results highlight the potential of HNK as an immunotherapeutic agent for mBCSCs, modulating the tumor's immune environment.
Phase 1 study of M2698, a dual p70S6KJAKT inhibitor, in patients with advanced cancer	Investigating the effects of M2698, a dual oral p70S6KIAKT inhibitor, in patients with advanced cancer who have failed standard therapies	101 patients were treated (M2698, n= 62; M2698/trastuzumab, n=13; M2698/tamoxifen, n=26). The patients were predominantly <65 years old, female, had performance status 1 and were heavily pre-treated.	M2698 was well tolerated. Combined with trastuzumab or tamoxifen, M2698 demonstrated anti-tumor activity in patients with advanced breast cancer resistant to several standard therapies, suggesting that it could overcome treatment resistance
AKT inhibition is associated with favorable changes in the immune profile in the tumor microenvironment of hormone receptor positive, HER2 negative breast cancer	Evaluation of the effects of AKT inhibition on the tumor microenvironment through analysis of tumor tissue from patients with operable hormone receptor-positive, HER2-negative breast cancer treated in a pre- surgical trial with the AKT inhibitor MK-2206.	Patients treated with MK-2206 versus control patients	Increased CD3+CD8+ density was observed in post- vs. pre-treatment tissue in patients treated with MK- 2206 vs, control (87 vs. 0.2%, p 0.05). MK-2206 was associated with higher expression of interferon signaling genes (e.g., IFI6, p <0.05) and lower expression of myeloid genes (CD163,p <0.05) in differential expression and gene set enrichment analyses. Higher expression of pro- apoptotic genes (e.g., BAD) was associated with MK-2206 treatment (p <0.05).

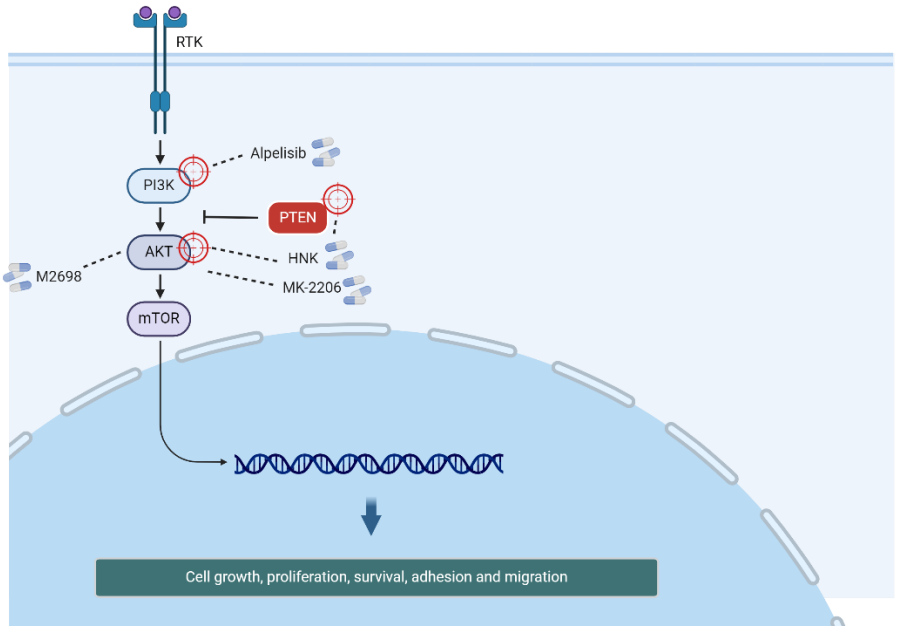

Fig. 2. Summary of the action of drug candidates on their target molecules
Source: author. Created with BioRender.com

Another study by Tsimberidou et al [17] reported the results of a phase 1 study in humans, with the use of M2698, an oral AKT inhibitor highly selective in AKT1 AND AKT3, in patients with advanced breast neoplasia, whose clinical picture was refractory to standard therapies, in addition to considering the safety and efficacy of M2698 in monotherapy or in combination with trastuzumab (anti- HER-2 monoclonal antibody) and tamoxifen. It was observed that M2698 was well tolerated both in monotherapy and in combination. Some advantages of using M2698 over the previously mentioned inhibitors have been reported, such as a more favorable and circumventable biosafety profile, reducing or excluding common adverse effects such as hyperglycemia, rash, hepatotoxicity and mucositis. Anxiety and abnormal dreams have been reported, but manageable with dose reduction. This may have been due to M298's penetrating properties in the blood-brain barrier, which on the other hand enables the treatment of brain metastases [17]. It has been reported that the association of M2698 can restore tumor sensitivity to hormonal therapy in the case of HR+ tumors and to trastuzumab in HER2+ tumors, making it a promising alternative to overcome cases of treatment resistance [17].

In the study by Marks et al [18], the authors identified the impact of AKT inhibition on the tumor microenvironment in an immunofluorescence analysis of biopsy tissue from patients with HR+/ HER2- breast cancer previously treated through a pre-surgical trial using MK-2206. They observed that patients who were treated with MK-2206, a treatment candidate drug with highly selective AKT action, showed a significant increase in the average density of cytotoxic T cells compared to control (untreated) patients, as well as greater expression of interferon signaling genes [18]. Through transcriptomic expression analysis, the effects of MK-2206 on the transcription of target genes of the PI3K/AKT/mTOR pathway were evaluated, and the mRNA confirmed the potential inhibitory activity of MK-2206 on the PI3K/AKT/mTOR pathway as well as low levels of expression of genes associated with cell cycle progression [18]. The study had a limited sample size due to adverse reactions presented by the population such as grade III rash, mucositis and pruritus [18].

Based on the articles reviewed, the new drugs being studied as PI3K/AKT/mTOR inhibitors can act by modulating the pathway, inhibiting the pathway and in the transcription of the pathway's target genes. The action of the new drug candidates in their specific molecules is exemplified in Fig. 2.

Some advantages can be seen in the use of these potential drugs compared to conventional

therapy, such as a reduction in adverse effects, an increase in the average density of cytotoxic T cells and greater expression of interferon signaling genes. On the other hand, some studies were only carried out in vitro or even only bioinformatics analyses, making it necessary to carry out *in vivo* studies. In addition, one study needed to reduce its sample size due to adverse reactions presented by the population with the use of MK-2206 [19,20,21,22].

Considering that the research focused on this subject is very recent (since 2020), this is characterized as a limitation of this study, since in view of all the searches and inclusion criteria, only 3 studies were selected for this review. It is noteworthy that the number of studies involving inhibition of the PI3K/AKT/mTOR pathway is growing, but the scientific evidence is still insufficient to provide an adequate answer as to the feasibility of its use in the case studied and the approval of new drugs capable of overcoming resistance to hormone therapy.

4. CONCLUSION

The drug candidates discussed in this review have good prospects as inhibitors of the PI3K/AKT/mTOR pathway. Two of the drugs reviewed act selectively on AKT (MK-2206; M2698), while HNK has a dual action on both AKT and PTEN. These targets differ from the drug traditionally used in hormone therapy, Alpelisib, whose mechanism of action is PI3K inhibition. Inhibition of the PI3K/AKT/mTOR pathway as an alternative to resistance to hormone therapy is a promising avenue to be explored, although the range of studies on this subject is insufficient to date. In this sense, new studies on the subject need to be carried out, especially in vivo studies, studies evaluating the biosafety profile and therapeutic efficacy of candidate drugs, as well as studies aimed at comparing the treatment of breast cancer at different stages and not only in metastatic cases.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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