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The Role of mTOR Inhibitors in Breast Cancer Treatment

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Short Communication

Breast cancer is one of the most common cancers in women in the world and its incidence is rapidly increasing. Mortality rates due to breast cancer are increasing significantly despite the innovations in diagnosis and treatment. It emerges as a problem that must be overcome for all units in the field of health. Expressed tumor markers are a heterogeneous disease due to different clinical and pathological characteristics. Although success is achieved as a result of surgical intervention, chemotherapy and radiotherapy in the treatment of breast cancers, development of resistance to treatments or relapse is generally observed due to the heterogeneous disease [1,2].

Response to therapeutic agents used in breast cancer varies due to the different genomic properties of cancer cells. Therefore, it is important to define malignant cells at genomic and molecular level in breast cancer. It is known that the PI3K/Akt/mTOR signaling pathway, which is effective in breast cancer development and metastatic process, plays an important role [2-4]. Overexpression of tyrosine kinases or mutations in signaling pathway components cause sustained activation of the PI3K/Akt/mTOR signaling pathway. This signal transduction pathway has many metabolic and physiological roles, from cell proliferation to invasion, from preventing apoptosis to angiogenesis, from tumor growth to metastasis [4,5]. The most important PI3K/Akt/mTOR signaling pathway mutations in breast cancer are mutations in the *PIK3CA* gene and are seen at a rate of 10% to 40% [2]. Another common mutation is mutations in Akt and they are seen at a rate of 5% to 24% [4]. *PIK3CA* mutations usually occur in ER^+ or HER2 amplified breast tumors, and this is considered to be a major determinant of resistance to endocrine and HER2-targeted therapies [3,6].

Studies have reported that inhibition of the PI3K/Akt/mTOR signaling pathway is important in the treatment of breast cancer. The PI3K/Akt/mTOR pathway contains multiple putative treatment goals. This makes targeted inhibition of members of this pathway, including PI3K, PDK-1, Akt, and mTOR, a potential strategy for breast cancer treatment. Many studies have found that PI3K/Akt/mTOR signaling pathway inhibitors have a synergistic effect when used together with chemotherapy, endocrine therapy (tamoxifen, raloxifen, etc.) and/or radiotherapy [3,6-12]. Numerous mTOR pathway inhibitors have been developed. One of these, Rapamycin, has been discovered more reliable analogues known as "rapalogists" due to its undesirable pharmacological properties. These; RAD001 (everolimus), CCI-779 (temsirolimus) and AP-23573 (deferolimus). In the BOLERO-2 study, it was reported that the addition of everolimus to exemestane provided better progression-free survival compared to women who only received exemestane, since it did not resist hormone therapy in patients with metastatic breast cancer [12]. Several novel treatment strategies with mTOR inhibitors are currently being investigated. Itamochi et al. [13] in their study on breast cancer cells; examined the effectiveness of cytotoxic drugs used in breast cancer such as cisplatin, doxorubicin, etoposide, paclitaxel, gemcitabine in combination with rapamycin. Rapamycin etoposide and doxorubicin combination creates a synergistic response; they stated that it produced an antagonist response in combination with paclitaxel and cisplatin [13].

As a result, breast cancer belongs to the complex and heterogeneous group of diseases. Different therapeutic methods are widely used in treatment including surgery, radiotherapy, chemotherapy, hormonal therapies and/or targeted therapies. In PI3K/Akt/mTOR breast cancer, the PI3K/Akt/mTOR signaling pathway is often over-activity. It is recognized as one of the most challenging pro-survival pathways resistant to cancer treatment. It seems that targeted therapies that are effective in these ways may also be effective in breast cancer. However, there are insufficient data regarding its role in breast cancer treatment. Determination of signal transduction pathways and their relationships in determining which group of patients to be used in breast cancer treatment may lead to the development of new treatment strategies.

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