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Summary of resistance mechanisms and therapeutic approaches in metastatic ER+ breast cancer

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Abstract:

Breast cancer is a prevalent malignant tumor in worldwide and it has been a prime challenge for public health. The development of this cancer is close related to drug use, breast cancer susceptibility genes, and diet. It can be categorized into four groups, which are 1. estrogen-containing receptor (ER+); 2. progesterone receptor (PR+); 3. with one or both receptors (HR+) and 4. HR- without these receptors. Estrogen receptor-positive breast cancers, ER+, are commonly produced when the level of estrogen in the breast cancer is higher than that which helps the cancer to grow and spread.[1]ER+ breast cancers have receptors and can use estrogen to grow, so common treatments are usually surgery and hormone therapy. This study will describe the mechanisms of endocrine therapy, the reasons why tumors become resistant to endocrine therapy, the progress made in recent years in overcoming resistance to endocrine therapy as well as suggesting undiscovered tactic to overcome this resistance in the future.

Keywords: breast cancer, endocrine therapy, estrogen-containing receptor (ER+), resistance

1. Introduction

1.1 Factors contributing to breast cancer.

A survey of women who have used birth control pills/estrogen replacement drugs found that these drugs cause breast enlargement and tenderness, and that the activity in the drugs, combined with a ‘’ high fat & low fiber’’ diet, which stimulates breast tissue and may induce breast cancer.

1.1.1 BRCA-1

BRCA-1, the breast cancer susceptibility gene is a breast cancer-producing factor that is carried over to the next generation through heredity. Studies have shown that a woman’s risk of developing breast cancer increases if some people in her family have a specific type of cancer. The risk is greatest if a family member had breast cancer as a teenager.

1.1.2 Diet

Breast cancer has a relationship with dietary fat above the standard intake and lack of certain nutrients. Specifically, animal fats may stimulate colon bacteria to form estrogen in dietary cholesterol thereby increasing estrogen levels in the body. Alcohol

consumption, obesity, and increased fat consumption can also be associated with cancer formation.

1.1.3 Obesity

Numerous studies have shown that an increase in body mass index (BMI) correlates with growth risk of breast cancer. Obese people have a higher risk of death for women who also tormented by breast cancer. For obese patients, estrogen levels increasing, aromatization of adipose tissue activating excessively, pro-inflammatory cytokines overexpressing, adipocyte-derived adipokines, hypercholesterolemia, and even excessive oxidative stress could be the factors that lead to the development of breast cancer. [6]

1.1.4 Alcohol

Ethanol metabolism and alcohol are also strongly causing breast cancer. Ethanol role as cell proliferation stimulator, enhances ERα and aromatase expression in breast cancer cells, confirming the use of ER signalling in breast cancer cell proliferation. Also, ethanol was proved that have ability to stimulate the proliferation of human ER+. MCF-7 and T47D cells, which are hormone responsive, ethanol stoichiometry correlates with ER-α activity and can lead to down-regulation of the expression of the tumor suppressor gene BCRCA1. [7]

1.1.5 Environment

It has been reported that women in areas with high levels of air pollution, especially lead and mercury, have a higher probability of developing postmenopausal breast cancer. Meanwhile, high concentration of nitrogen dioxide is related to higher risk of breast cancer. Radon gas, a naturally occurring substance in the environment, can break down into radioactive particles and bind to air pollutants, and these radioactive particles have been linked to a higher risk of oestrogen receptor invisible breast cancer.

1.2 Characteristics of Er+ breast cancer

After diagnosis of breast cancer, the patient may undergo further tests to determine the receptor status. Up to today breast cancer can be categorized into two groups, hormone receptor positive or negative, judgement of them will depend on whether the patient has estrogen receptor proteins/ progesterone receptor proteins. These are ER+ for estrogen-containing receptors, PR+ for progesterone receptors, and HR+ for having both of the receptors, as well as HR- without these receptors. In other classifications, cancers may also be classified as HER2 + or -. This estimation depends on HER2, which is a protein that promotes the growth of HER2-positive breast cancers and its cells with higher-than-average levels of HER2.

Among other things, ER+ breast cancer happens when high levels of estrogen assist the cancer to spread. Cells in the body have hormone receptor proteins. Estrogen can attach to these receptors. This process is part of the body's function, often occurs in blood. In healthy cells, ER help cell function and growth. However, ER-positive breast cancer occurs when estrogen binds to proteins in cancer cells, causing the cells to grow. Cosmetically, chest features in patients with ER+ include size changing, shape deformity; lumps grow in the chest, near the breast or armpit. Sometimes also include nipple's look and feel changes.

2. Common treatments for ER+ breast cancer

2.1 Breast Surgery

Mastectomy is traditionally the standard treatment for breast cancer. It can be categorized into three categories: removal of the cancerous area, removal of the total breast and removal of the lymph nodes.

The removal of the area of cancer can be also called as breast conservation surgery and lumpectomy or wide local excision, where the surgeon aims to remove the border between the cancer and the surrounding healthy tissue. Size and location of the cancer need to be considered if patient choose the entire mastectomy, whether breast reconstruction will be an important determining condition. Lymphadenectomy is because cancer cells can separate from the breast tissue and travel to other parts of the body, in which case they generally spread preferentially to the lymph nodes in the armpit close to the breast. Before this procedure is performed patients will have an ultrasound scan to detect the lymph nodes in the armpit near the breast. A biopsy is also performed to determine if they contain cancer cells. In addition to the lymph node removal surgery, the other two types of surgeries continue to be followed by a personal decision about whether radiotherapy is needed.

Many people choose to have breast surgery that preserves the breast and removes the tumor without removing healthy breast tissue for personal reasons. Despite its high success rate, it is not suitable for female at high risk of local recurrence. At the same time, there are several conditions that must be met for local excision: localized tumor, no inflammatory cancers, no history of radiotherapy to the breast or chest, etc.

2.2 Radiation Therapy and Chemotherapy

Radiotherapy and chemotherapy are treatments based on organ preservation. This therapy technically alleviate cancer by killing cancer cells and depress their growth by devastating their DNA. DNA damaged cancer cells will

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then stop dividing or die, and removed by the body after broken down. This treatment is more expensive than other treatments and is often associated with serious side effects. For example, fatigue and weakness, skin problems, breast swelling, and often hair loss in the treatment area, and so on.

2.3 Endocrine therapy

Endocrine therapy is also known as hormone therapy which rely on hormones, which are substances produced by the body that handle the growth and activity of most of the cells. They can stimulate to help some breast cancer cells growing, and this therapy works by 1. reducing the number of hormones in the body. and 2. organizing their entry into the breast cancer cells. Hormone therapy can reduce the level of oestrogen or progesterone in the body or stop its effects. The effect of hormone therapy may limit to be effective when the breast cancer cells have oestrogen receptors.

Endocrine therapy is usually started after surgery or chemotherapy as an adjuvant treatment to reduce the risk of recur. The typical duration of hormone therapy is five years and depends largely on the type of medication available, the individual's circumstances and the side effect it produces. Endocrine therapy before surgery is known as neoadjuvant therapy and is used to try to shrink large cancers to allow surgery to remove smaller parts. Giving patients the opportunity to choose lumpectomy over mastectomy. For women who are physically unable to have surgery, hormone therapy will be the primary treatment to control the size of the cancer.

Endocrine therapy usually uses Selective estrogen receptor modulators, Aromatase Inhibitors and Selective Estrogen Receptor Down-regulator. This therapy prevents the production of estrogen or blocks estrogen, which prevents the stimulation of estrogen sensitive tumors. stimulation of oestrogen-sensitive tumors. However, drug resistance remains a major problem.

3. Resistance to endocrine therapy

While endocrine therapy, the primary treatment for ER+ breast cancer, has been able to dramatically reduce breast cancer mortality, it has also been shown to be progressively less effective as advanced tumors develop resistance to it. This has led to the fact that breast cancer recurrence and acquired resistance remain a main problem worldwide. A growing amount of resistance regimes have been reported, including somatic alterations, epigenetic changes and changes in the tumor microenvironment.

As for the focus of this study, the estrogen receptor in ER+ breast cancer is overwhelmingly rely on the activation of ER by rachitic hormones. Estrogen negative induced activation of Era and Erb nuclear receptors improve proliferation and survival of both normal and cancerous breast tissues through genomic and non-genomic regulation thereby. [2] Upon binding to estrogen, ER dimerizes and translocate to the nucleus. In this tissue, the dimer forms transcriptionally active ER complexes by binding to coactivators. ER negatively bound to estrogen induces cell cycle progression through induction of the cell cycle protein D1. In addition to this, estrogen-stimulated ER approaches mitogenic signaling as they can upregulating the transcription of growth factors (which play an essential role in mammary gland development). The estrogen ER driver that controls normal mammary gland development is also responsible for regulating breast hyperplasia, tumorigenesis. And of these, estrogen inhibition and ER antagonists are the pillars of treatment for ER+ breast cancer.

4. Mechanisms of endocrine therapy

Hormone therapy reduces the number of specific hormones in the body and prevents certain hormones from reaching breast cancer cells. Using hormone therapy before surgery can help shrink the cancer and the chances of the cancer coming back after surgery are reduced. Endocrine therapy can be divided into four categories:

4.1 Aromatase Inhibitors (Ais) [3] deplete systemic oestrogen levels in postmenopausal patients by blocking the conversion of androgens to oestrogens. It can be divided into two categories, the first being non-steroidal AIs, including Anastrozole and Letrozole, whereas Exemestane is a Steroidal AI, where irreversible inhibition of the aromatase enzyme requires the production of new aromatase to overcome the inhibition.

4.2 Selective estrogen receptor modulators (SERMs) [3] compete with estrogen in order to bind with the ER. Have abilities of mixing agonist/antagonist. And SERMs have tissue-specific activity. Commonly is more suitable for use in premenopausal and postmenopausal female primarily in premenopausal patients.

SERMs include Tamoxifen (TAM) [3] a selective estrogen receptor modulator. TAM can exert anti-estrogenic activity in the breast and vaginal mucosa by inhibiting ER dimerization. However, as a side effect, TAM promotes endometrial hyperplasia, blood clots, and has estrogenic effects on bone, lipids, and liver.

4.3 Selective Estrogen Receptor Down-regulators (SERDs) [3] are found to work mainly by inducing ER protein degradation or blocking ER transcriptional activity. Among these, Fulvestrant, an agent with anti-estrogenic effects restricted to postmenopausal women, suppressed

ER dimerization and ultimately leads to downregulation of ER expression. It is classified as a selective estrogen receptor down-regulator.

Recently, it has been found that the inhibitory effect of SERD results from the decreased capability of SERD-bound ER to translocate to the nucleus. In addition, the complex of ER and SERD is failed to make an open chromatin conformation for facilitate transcription of ER-regulated genes. SERD-ER binding is degraded by impaired mobility.[3]

5. Mechanisms of drug resistance

Drug resistance can be thought into two main groups: primary and secondary. Primary resistance is mainly due to loss of ER expression, whereas secondary resistance is mainly due to ESR1 mutations, oncogenic phosphatidylinositol 3-kinase (PI3K)/Akt pathway, altered mitogen-activated protein kinase (MAPK) pathway and tumor microenvironment.[4]

Endocrine resistance is usually driven by ligand-independent reactivation of the ER. This can occur through gain-of-function mutations in the ER, altered interaction of the ER with coactivators/co-inhibitors, or compensatory crosstalk between the ER and growth factor receptors and oncogenic signalling pathways. In adapting and/or resisting to anti-estrogens, growth factor-driven mitogenic and survival pathways may reactivate ER-mediated transcription in the absence of estradiol. These resistant tumors are often relied on aberrantly activated survival pathways and the ER. In most cases. The combination inhibition of both pathways gives more substantial results.

6. Antidrug resistance programmes

The use of CDK4/6 inhibitors has changed the treatment of ER+ MBC utterly. Current agents such as palbociclib, abemaciclib and libociclib. They are allowed to the treatment of ER+ in the first line setting in combination with endocrine therapies. The use of CDK4/6 inhibitors to ET has dramatically improved PFS and overall survival.[4]

Everolimus. An inhibitor of mTOR. One mechanism of endocrine resistance involving the PI3K/Akt pathway is ligand-independent activation of ER. S6 kinase, which is a substrate of mTOR complex 1, phosphorylates activating functional structural domain 1 (AF1) of ERα. Everolimus binds to and heterodimerically depressing mTORC1, defeating this resistance mechanism.[4] In addition, fulvestrant may be a more appropriate anti-estrogenic companion to everolimus in patients with disease progression after AI. And fulvestrant or tamoxifen has been listed as additional partner options to everolimus, published by the National Comprehensive Cancer Network guidelines.

Pemetrexed. A protein kinase inhibitor targeting the PI3K pathway, which effectively inhibits abnormal activity of the PI3K pathway in tumor cells to slow or inhibit tumor growth.[4]

7. Future directions

The CDK4/6 inhibitor, as an important player that has transformed the treatment of ER+ breast cancer, should undoubtedly receive more attention in the future. Instead, researchers' efforts should be invested in preventing resistance to combinations of endocrine therapy and CDK4/6i. Combinations of CDK4/6 inhibitors with AI or fulvestrant should be given more focus as the current standard first-line treatment option.

In addition to this, studies have shown that inhibition of carbidopa as an aromatic amino acid decarboxylase is likely to be able to reduce the incidence of most cancers, including breast and pancreatic cancers. Experimentally, carbidopa has been shown to be strongly selective for ER+ breast cancer cells, while ERα is a potential target whose levels are reduced by the presence of carbidopa. Therefore, the potential of carbidopa in ER+ breast cancer should also be appreciated, and it is very likely that it will be added to combination therapy as prevention or control of breast cancer.[5]

8. Conclusion

The above summarizes the ways of drug resistance and treatment of metastatic oestrogen receptor-positive (ER+) breast cancer, which is one of the most popular type of breast cancer, the treatment of which heavily depends on endocrine therapies, but resistance to these therapies has emerged as a major challenge. The study details the mechanisms of endocrine therapy, including the use of drugs such as aromatase inhibitors (AIs), selective estrogen receptor modulators (SERMs), and selective estrogen receptor down-regulators (SERDs). Resistance arises due to loss of ER expression, ESR1 mutations, and alterations in the PI3K/Akt and MAPK signalling pathways. To overcome drug resistance, strategies such as the combination of CDK4/6 inhibitors and the mTOR inhibitor everolimus have been proposed. For future research directions, such as further investigating the combination of CDK4/6 inhibitors with endocrine therapy and exploring the potential of new drugs such as carbidopa.

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