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RESEARCH ARTICLE

HORMONE THERAPY FOR BREAST CANCER

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ABSTRACT

Background: Breast cancer is the most common cancer in women worldwide. Most women with newly diagnosed breast cancer are of luminal type.
Aim: To explore the modern modalities focusing on the hormone therapies for breast cancer.
Methods: Systemic review of PubMed filter finds publications to support keywords of the current study.
Findings: Treatment of breast cancer can be classified into local or systemic therapies. Local therapies like Surgery, Radiotherapy, However systemic treatment includes chemotherapy, Targeted therapy by anti-HER2 blockade and endocrine treatment that involves selective estrogen receptor modulators (SERM), aromatase Inhibitors (AI), fulvestrant, and ovarian suppression. Recent studies recommends that higher-risk patients should receive ovarian suppression in addition to adjuvant endocrine therapy, whereas lower-risk patients should not. Women with stage II or III breast cancers who would ordinarily be advised to receive adjuvant chemotherapy should receive ovarian suppression with endocrine therapy.
Conclusion: Hormonal therapy of breast cancer is personal, women with stage I breast cancers not warranting chemotherapy should not receive ovarian suppression, nor should women with node-negative cancers 1 cm or less. Ovarian suppression is effective and may be administered with either tamoxifen or an aromatase inhibitor.

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INTRODUCTION

Breast cancers originate in the mammary gland (1). It is the most common type of cancer in women after skin cancer (2). The incidence of breast cancer increases dramatically with age (3). It is higher in industrialized countries than in most developing countries of the world (4). It could be due to differences in hereditary and life-style factors (5). The most important risk factor is life-time exposure to female sex hormones. Age at menarche, menopause and first pregnancy therefore affect the risk. Increased risk is also correlated to hormone replacement therapy, oral contraceptives, obesity and height. Breast feeding, on the other hand, reduces the risk (6). An increased risk has been related to previous benign breast disease, alcohol intake and prior exposure to radiation. Another important risk factor is a family history of breast cancer (7). The most well-known high-risk genetic predisposition arises from mutations in the BRCA1 or BRCA2 gene. The prevalence of these mutations among breast cancer patients varies with geographic location and the patient's age and family history. Inherited mutations in p53 and PTEN are also associated with syndromes that include a high risk of breast cancer, although these syndromes are rare. Studies on twins suggest that 20-30% of all breast cancer is due to genetic predisposition, and a woman's risk of developing breast cancer is increased by a factor of two if she has a first-degree relative with the disease. The more cases in the family and the younger the relatives were when they developed breast cancer, the higher the risk (8). For every five incidences of the disease, two deaths occur. The high incidence, the complexity and the cost of the treatment make breast cancer one of the most relevant health problems in the society. Breast cancer disseminate at different stages, for example, in some patients the dissemination could take years while in others this could take only weeks based on how aggressive the tumor is. For better prognosis and survival rate, the tumor should be detected

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while it is still small in size, has not metastasized yet and probably non-invasive. Based on the tumor characteristics and the patient's condition the treatment is determined, although some invasive tumor may regress spontaneously (9). There is a decline in the mortality rate of the breast cancer during the past twenty years, this is due to the early diagnosis of the cancer and the efficacy and the improvement of the treatment (10). The widespread of population based screening program allowed an early diagnosis and consequently higher rates of curability. In addition to better staging procedures and improvement in the radiation, surgery, chemotherapy and hormonal therapy, all lead to better controlling the cancer and minimize the mortality rates (11,12,13,14).

Signs and symptoms

Many early breast carcinomas are asymptomatic (15). Larger tumors may present as a painless mass. Only 5% of patients with a malignant mass present with breast pain. Breast cancer is often first detected as an abnormality on a mammogram before it is felt by the patient or the doctor (16). Signs and symptoms indicating the possibility of the presence of breast cancer can be:Skin changes (thickening, swelling, or redness), change in breast size or shape, nipple discharge, particularly if bloodstained, and recent nipple inversion or other nipple abnormalities (ulceration, retraction, or spontaneous bloody discharge) (17). Axillary lump which is a suspicious mass that detected by screening or by palpation, a combination of three diagnostic modalities is used: Clinical examination of the breast and loco-regional lymph nodes, radiologic examination combined with ultrasound, and in some cases magnetic resonance imaging (MRI), and histological examination of fine-needle aspirates, often supplemented with a core biopsy (17,18,19).

Histological types of breast cancer

Some types of the breast cancer start in the epithelial cells that line the breast and they are called carcinoma. The carcinoma that starts in the glandular tissue are called adenocarcinoma, these are the most common type. There are some other types like sarcomas which start in the muscles, fat, or connective tissue (20,21,22,23).

Ductal carcinoma in situ (DCIS)

90% of breast carcinomas arise in the ducts of the breast. They begin as atypical proliferation of ductal epithelium that eventually fill and plug the ducts with neoplastic cells (24). As long as the tumor remains within the confines of the ductal basement membrane it is classified as DCIS. Localized DCIS is impalpable but often visible on mammography as an area of microcalcification. Not all DCIS will inevitably progress, but the probability of development of invasive cancer is estimated at 30–50% (25,26).

Invasive ductal carcinoma

This accounts for 70-80% of breast cancers. The malignant cells are associated with a fibrous stroma which can be dense (scirrhous carcinoma). The tumor invades through breast tissue into the lymphatics and vascular spaces, to gain access to the regional nodes (axillary and, less often, internal mammary) and the systemic circulation (27). The histological grade of the tumor is assessed from three features (tubule formation, nuclear pleomorphism, and mitotic frequency), and predicts the behavior of the tumor. Estrogen and progesterone receptor status is commonly assessed by immunocytochemistry. Other biological markers (e.g. c-erbB2) may be of value both as a predictor of prognosis and as a guide to therapy (28,29,30).

Ductal carcinoma of special type

A number of pathological variants are identified with relatively good prognosis, namely medullary carcinoma, tubular carcinoma, and mucinous carcinoma. Paget's disease of the breast is ductal carcinoma of the excretory ducts with involvement of the skin of the nipple and areola (31).

Lobular carcinoma in situ

These pre-invasive lesions carry a risk not only of ipsilateral invasive lobular carcinoma but also of contralateral breast cancer. They typically are neither palpable nor contain microcalcification. Marked pleomorphism, atypia and mitotic activity are usually absent. It is often multifactorial in nature and it is more of a marker rather than a precursor, and this is due to the fact that women diagnosed with LCIS have a marked increase in the risk of developing invasive lobular or ductal carcinoma in their lifetime (32).

Invasive lobular carcinoma

Lobular carcinomas account for 5–10% of breast cancers. About 20% develop a contralateral breast cancer, and tends to be multicentric within the same breast, with a diffusely infiltrative pattern. Grossly the tumor appears rubbery and poorly defined or gritty hard with infiltrating borders (33).

Hormone receptors in breast cancer

Beatson has shown in 1896 that hormones are associated with breast cancer since oopherectomy resulted in tumor regression (34). Estrogen plays an important role in the growth of breast cancer. It binds to the estrogen receptor (ER), leads to dimerization and conformational changes which then leads to the proliferation of the tumor cells. The majority of breast cancers around 75% are (ER+), some types of breast cancer may express progesterone receptor (PR+) (35,36). The ovaries are the main source of estrogen in premenopausal women, however in postmenopausal women estrogen is still secreted by the adipose tissue, and by the conversion of androgen secreted by the adrenal gland into estrogen. The incidence of hormone related breast cancer is higher in developed and developing countries rather than rural areas. It is very high in North America, North and West Europe, intermediate in South Europe and South America, and the lowest in Africa and Asia (37,38,39).

Estrogen receptor

The ER is an intracellular receptor which belongs to the steroid nuclear receptor super-family of transcription factors. The

receptor contains two activation domains: activation function AF1, which is regulated by phosphorylation, and activation function AF2, which is regulated by estrogen binding. AF1 and AF2 can activate transcription individually and or synergistically. Binding of estrogen to the ER leads to a conformational change in AF2, facilitating interaction with coactivators and histone acetyltransferases. In complex with these factors the ER then activates gene expression on a nuclear level. This can be done by direct dimeric binding of the ER to specific DNA response elements, so-called estrogen response elements (EREs). It can also take place through interaction with other transcription factors, such as activation protein 1 (Ap1) and specificity protein 1 (Sp1). Apart from the classical ligand-bound pathway, the ER can be activated by signaling events downstream of receptor tyrosine kinases, such as HER2 (40,41,42,43,44).

Treatment of breast cancer

The treatment of breast cancer can be classified into local or systemic therapies. The local therapy treats the tumor in its site without affecting the rest of the organs, and this can be achieved by surgery and radiation. The systemic therapy can affect other tissues and organs in the body, the route of the drug administration can be oral or directly into the bloodstream. Chemotherapy, hormonal therapy and targeted therapy are all examples of systemic therapy. The treatment of the breast cancer can be also classified into adjuvant and neoadjuvant therapy. Adjuvant therapy is given to the patient after the surgery to help to prevent cancer recurrence. Radiation and systemic therapy can be used as adjuvant therapy. The neoadjuvant therapy is given to the patient before the surgery, and this is to shrink the tumor. Some patients who receive neoadjuvant therapy may also need adjuvant therapy (45,46,47).

Local treatment

Surgery

Surgery is the primary treatment for early-stage breast cancer; many patients are cured with surgery alone (48). The goals of breast cancer surgery include complete resection of the primary tumor with negative margins, and for a pathologic staging of the tumor and axillary lymph nodes (ALNs). This will help to provide the necessary prognostic information. Sentinel lymph node biopsy (SLNB) is a minimally invasive procedure in patients who have clinically negative node. In this procedure the sentinel lymph node is excised and examined to determine whether the tumor has the ability to spread and metastasize. The result can be negative which means that the tumor did not spread to other lymph node, or it can positive which means that the tumor has spread to other lymph nodes or other organ (49,50,51). Total mastectomy is a procedure where the total breast tissues are removed, the nipple and areola are also removed. A modified total mastectomy is a procedure similar to the total mastectomy but also involves the dissection of the axillary node. Other new variation of total mastectomy are skin sparing total mastectomy (SSM), and nipple sparing total mastectomy (NSM) (52). Radical mastectomy involves the removal of the entire breast tissues, axillary lymph node and pectoralis major muscles (53). In the 1980s, breast-conserving therapy became the treatment of choice for patients with early breast cancer (54).

Radiotherapy

Radiation therapy is treatment with high-energy rays or particles that destroy cancer cells. Postoperative radiotherapy is administered in order to eradicate possible residual microscopic disease and help lower the recurrence rate. Radiation therapy can be given externally as in external beam radiation or internally as in brachytherapy. According to international guidelines, radiotherapy is indicated if the risk of developing a local recurrence within the next 20 years is higher than 10%. This includes women undergoing partial mastectomy, women with a tumor larger than 50 mm and women with more than three lymph node metastases in the axilla. Acute side effects of radiotherapy are erythema of the skin and pneumonitis. Late side effects include brachial plexus neuropathy and lymphedema (55,56,57).

Systemic treatment

Chemotherapy

Poly-chemotherapy has proven to be more effective than single-agent regimes in neoadjuvant and adjuvant settings. The reasons for this are the potential synergetic effects and the different toxicity profiles, allowing more intense treatment. Adjuvant treatment with poly-chemotherapy reduces breast cancer mortality by about one third. Comparisons between different regimes have shown anthracycline-based therapy to be more effective than CMF (cyclophosphamide, methotrexate, fluorouracil), and the addition of a taxane to anthracycline-based therapy to be more effective than anthracyclines alone. Adjuvant chemotherapy is today recommended for most patients with lymph-node-positive disease, and for patients with lymph-node-negative disease if the tumour exhibits a low sensitivity to endocrine treatment, or if other risk factors are present (58,59,60).

Targeted therapy: anti-HER2 blockade

Targeted therapy are medications disrupting specific molecules involved in carcinogenesis and tumor growth, rather than generally affecting rapidly dividing cells, as is the case in most of the chemotherapies. The monoclonal antibody trastuzumab is directed against the human epidermal growth factor receptor 2 (HER2) oncogene product, which is expressed in 15-30% of breast cancers (61,62).

Endocrine treatment

Hormonal therapy is a type of a systemic therapy. It can be used as an adjuvant therapy, neoadjuvant therapy or in metastatic cancer. Although it can be very effective, it will only work if the breast cancer is hormone dependent. There are many types of hormonal therapies, and most of these types work mainly by either blocking the estrogen from binding to the estrogen receptors or by lowering the estrogen in the body. This will be discussed in more details in the next chapters (45,63).

There are 4 major classes of endocrine therapies

1. Selective estrogen receptor modulators (SERM) (64).
2. Aromatase Inhibitors (AI) (65).
3. Fulvestrant (66,67).
4. Ovarian suppression (limited to premenopausal patients) (68).

Selective Estrogen Receptors Modulators (SERM)

There are three classes of selective estrogen receptors modulator drugs: Tamoxifen, Raloxifene, Toremifene. They are competitive inhibitors of estrogen binding to estrogen receptors. They all have mixed agonist and antagonist effects depending on the target organ. SERMs block AF2 activity, they may act as estrogen antagonists in cells where AF2 plays a major role in ER transcriptional activation. In cells where AF1 is more important, however, they may have estrogen-like effects. Agonist/antagonist effects are also dependent on the type and ratio of coactivators and corepressors expressed, and the gene promoter specific recruitment of these factors. Another influencing factor may be the distribution of ER-α and ER-β in the tissue (64,69).

Aromatase Inhibitors (AI)

Aromatase Inhibitors work by blocking the enzyme aromatase which is present in the fat tissue from converting a small amount of androgen into estrogen in the body. This will lead to a small amount of estrogen available to the hormone receptor positive breast cancer. The Aromatase Inhibitor drugs cannot stop the ovaries from producing estrogen, so in order for this drug to work the patient has to be a postmenopausal woman (65). Studies showed that switching to an aromatase inhibitor after taking Tamoxifen for 2 to 3 years (for a total of 5 years of hormonal therapy) offers more benefits than 5 years of Tamoxifen. Taking an aromatase inhibitor for 5 years after taking Tamoxifen for 5 years continues to reduce the risk of the cancer coming back, compared to no treatment after Tamoxifen. It is the best hormonal therapy to start with in early stage of a hormone receptor positive breast cancer, it has more benefits and fewer side effects than Tamoxifen, such as blood clots, stroke, and endometrial cancer. But Aromatase Inhibitors can cause increase the bone thinning and turnover which lead to bone loss (osteoporosis), more heart problems, and more broken bones than Tamoxifen, at least for the first few years of treatment. The patient is advised to do a bone density test to check the condition of the bone to see whether it is necessary to take a bone strengthening medication or not. The most common side effects of Aromatase Inhibitors are joint stiffness or joint pain which can be troubling. Other common side effects of Aromatase Inhibitors drugs are related to estrogen deprivation such as vaginal dryness, night sweats and hot flashes. Some studies have shown also that taking an Aromatase Inhibitors drugs can decrease the risk of breast cancer in a postmenopausal women who are at high risk (65,70,71).

Fulvestrant

This drug is a synthetic drug, selective estrogen receptor down regulator (SERDs) is also termed 'pure anti-estrogens, has a complete antagonist effect on the estrogen receptors with no agonist effects at all (unlike Tamoxifen which has a partial agonist effect). In addition it increase the rate of the estrogen receptors degradation, which can lead to stop or slow the growth of some tumor cells which need estrogen to grow, unlike Aromatase Inhibitors (which decrease the level of the estrogen available to the tumor cells). It binds competitively to the estrogen receptors in the breast cancer cells resulting in deformation of the estrogen receptors and reduce estrogen binding. It has a higher affinity for the estrogen receptor (ER) compared to SERMs. It is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women. Used as a second line therapy in case the postmenopausal woman has relapsed or progressed after a previous hormonal therapy. It can be administered by the doctor the nurse since it is an injection (intramuscular injection IM) in the buttock muscle. Initially It is given every 2 weeks for the first 3 doses and then It is given once a month as a single dose or it can be divided into two doses. Side effects are often predictable in terms of their onset and duration, and they are almost always reversible after treatment is complete (66,67,72,73).

Ovarian suppression

In premenopausal women estrogen levels can be dramatically reduced by ovarian ablation. This can be achieved surgically by oopherectomy, by radiotherapy or by using LHRH (luteinizing hormone-releasing hormone) agonists to suppress ovarian function(68,75). Ovarian ablation has been found to significantly reduce recurrences and breast cancer mortality. LHRH agonists significantly reduce the relative risk of recurrence by 12.7%, and death by 13.6%, when given in combination with Tamoxifen, chemotherapy or both (43). Treatment with a LHRH analogue could be considered when there are contradictions for chemotherapy. LHRH agonists also show a small additional benefit when used together with chemotherapy, but only in the youngest premenopausal patients, <40 years old (76). The American Society of Clinical Oncology endorsed guidelines recommending that ovarian ablation or suppression (hereafter, ovarian suppression) not be added routinely to adjuvant therapy in premenopausal women.

Conclusion

Endocrine treatment of ER-positive breast cancer with Tamoxifen, Aromatase Inhibitors and Fulvestrant with or without ovarian suppression, was the first target-based therapeutic strategy. Unfortunately, a substantial proportion of patients, are either primarily resistant or will develop resistance during the course of their disease. It has become apparent that ER transcriptional actions are not just determined by the ligand, but also by complex interactions between co-regulatory molecules and multiple signaling pathways, which provide several potential mechanisms by which cancer cells may become estrogen-independent and Tamoxifen-resistant. Some pharmacological agents targeting these pathways are currently clinically available and others are in development, but it is imperative to remember that there are likely to be several clinically significant pathways to resistance and that some will be important in certain patients but

irrelevant in others. Resistance to SERMs, Aromatase Inhibitors, and SERDs are likely to be mediated by distinct pathways, which explains the lack of cross-resistance between the different classes of drugs. Combinatorial therapies of Tamoxifen (or other hormonal agents) with drugs aimed at the signaling pathways underlying the development of resistance may be a potential means of delaying the onset of resistance. A number of clinical trials have sought to determine whether the addition of signal transduction inhibitors to endocrine therapy may overcome endocrine resistance or delay its development. Trials using HER2/neu antagonists, tyrosine kinase inhibitors, multikinase inhibitors, src inhibitors, and mTOR antagonists are currently underway in the treatment of breast cancer. Understanding the mechanism of estrogen receptor resistance is very important in improving the treatment of a patient with breast cancer, and important for developing newer drugs and treatment strategies.

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