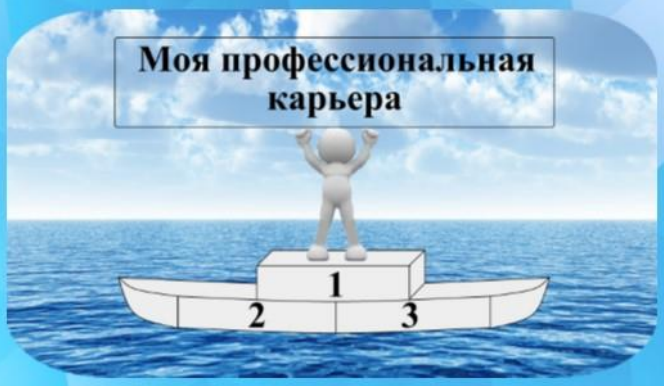

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ОБРАЗОВАНИЕ И НАУКА В XXI ВЕКЕ

Выпуск №24 (том 2)
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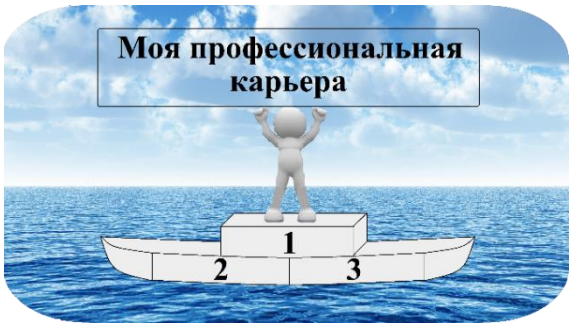

Международный научно-образовательный электронный журнал
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Миссия научно-образовательного электронного журнала «ОБРАЗОВАНИЕ И НАУКА В XXI ВЕКЕ» состоит в поддержке интереса читателей к оригинальным исследованиям и инновационным подходам в различных тематических направлениях, которые способствуют распространению лучшей отечественной и зарубежной практики в интернет пространстве.

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Материалы публикуются в авторской редакции. За соблюдение законов об интеллектуальной собственности и за содержание статей ответственность несут авторы статей. Мнение редакции может не совпадать с мнением авторов статей. При использовании и заимствовании материалов ссылка на издание обязательна.

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Название публикации: «MODERN ENDOCRINE THERAPY IN LOCALLY ADVANCED ESTROGEN OR PROGESTERONE RECEPTOR-POSITIVE BREAST CANCER»

Abstract

Breast cancer is the most common cancer affecting women, with a one in seven lifetime risk. Estrogen receptor-positive (ER-positive) breast cancer is the most common type of breast cancer diagnosed today.Each year, approximately two million women are diagnosed with breast cancer worldwide. Estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive breast cancer accounts for approximately 70% of all breast cancers, and 85% of those in women over 70 years of age. At the time of diagnosis, 7 to 20% of women will present with locally advanced breast cancer (LABC).According to the American Cancer SocietyTrusted Source, about 2 out of every 3 cases of breast cancer are hormone receptor-positive. BC in the territory of the Republic among urban and rural population by determining the average annual intensiveand standardized incidence rates for the years 2008 2010. The highest standardized incidence rates registered in Tashkent city (22,5%), Nawojski (12,4%up), Bukhara (11.190) and Tashkent regions (11,0%) and lowest in Surkhandarya (6,35)and Kashkadarya (7,5%). On the territory of the Republic those in urban areas more often suffer from cancer of the breast(13,2%) than rural (8,5%upool. The highest incidence was within the age intervals 50-59- 18,04609, 60-69 — 31.29, 70 years and older - 19.39%.[52]. Most of these cases are ER-positive,

meaning that there are estrogen receptors on the surface of the cell that bind to estrogen.This cancer typically responds to hormone therapy. Your prognosis will depend on what stage the cancer is in when you're first diagnosed and how well your body responds to treatment. ER-positive breast cancers can have a favorable outlook when they're treated early.

Keywords: breast cancer, Estrogen receptor-positive, progesterone receptor (PgR)-positive breast cancer, endocrine therapy, locally advanced breast cancer (LABC)

Introduction

The treatment of breast cancer has evolved considerably over the last two decades, leading toward individualized disease management. Hormone-sensitive breast cancers constitute the vast majority of cases and endocrine therapy is the mainstay of their treatment. On the other hand, neoadjuvant or pre-surgical treatments provide a number of advantages for tumor management

Endocrine therapy (ET) has established itself as an efficacious treatment for estrogen receptor-positive (ER+) breast cancers, with a reduction in recurrence rates and increased survival rates. The pre-surgical approach with chemotherapy (NCT) has become a common form of management for large, locally advanced, or high-risk tumors. However, a good response to NCT is not usually expected in ER+ tumors. Good results with primary ET, mainly in elderly women, have encouraged studies in other stages of life, and nowadays neoadjuvant endocrine treatment (NET) has become a useful approach to many ER+ breast cancers. The aim of this review is to provide an update on the current state of art regarding the present and the future role of NET.

Estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive breast cancer accounts for approximately 70% of all breast cancers, and 85% of those in women over 70 years of age.At the time of diagnosis, 7 to 20% of women will present with locally advanced breast cancer (LABC). LABC is defined as tumors that are > 50 mm in size or involve the skin of the breast/chest wall, multiple axillary lymph nodes, or the supra/infraclavicular lymph nodes [47]. The percentage of patients diagnosed with LABC in a particular population is largely dependent of the rate and effectiveness of mammography screening [29, 44]. Data from the USA shows that LABC is more likely to affect racial or ethnic minority groups, in particular African Americans, where 12% are diagnosed with LABC compared to 8% in white American

populations [21, 29]. This likely results from health inequities such as poverty, rurality, and reduced rates of health insurance which create barriers in accessing health care programs such as preventative screening [11, 29]. Women under the age of 40 may also be more likely to present with LABC as mammography is not routinely recommended in this group [29]. Similarly, on a global scale, LABC is more likely to be diagnosed in under-developed countries, where rates of LABC can reach up to 60% [29, 12, 15].

ET is a key pillar in the treatment of ER+ tumors, since it has widely demonstrated its efficacy in improving survival and reducing recurrences. In recent years, the neoadjuvant or presurgical approach has established itself as a very useful strategy in breast cancer management, because it offers numerous advantages. In the first place, tumor downstaging may be achieved, thus increasing breast-conserving surgery (BCS) rates and, in some cases, reducing axillary dissection[3.9].On the other hand, assessing the in vivo response enables us to determine drug efficacy, as well as to study any biological or molecular changes that may lead us to explore new biomarkers. Finally, neoadjuvant treatment provides a unique opportunity for validating new treatments, alone or in combination, given that results can be obtained in short periods of time. These advantages have established neoadjuvant chemotherapy (NCT) as a widely accepted approach to estrogen receptor negative (ER−) tumors, but neoadjuvant endocrine therapy (NET) still remains an underutilized tool for ER+ breast cancers, and is frequently relegated to the treatment of elderly or frail patients who are not candidates for chemotherapy. [14].

Breast cancer, for the majority of patients, is treated with upfront surgery followed by other adjuvant (post-operative) modalities including radiotherapy, chemotherapy, or endocrine therapy [15, 30]. However, for women with LABC, breast-conserving surgery (BCS) is not an option at the time of diagnosis, and there is potential benefit in a neoadjuvant, or pre-operative approach, to chemotherapy or endocrine treatment. The goal of neoadjuvant therapy is to reduce the pre-surgical tumor burden and increase the rate of BCS in mastectomy candidates, or allow operability of a previously inoperable tumor [2, 39]. The advantages of BCS include a reduction in surgical morbidity and mortality and improvement in cosmetic outcomes [30]. Neoadjuvant approaches also provide prognostic and predictive information [2, 20, 49].

Despite ER^+ breast cancer being the most common subtype of breast cancer [16], clinical guidelines for the neoadjuvant treatment of patients with ER^+ LABC are inconsistent or lacking in most settings. There are data to suggest that neoadjuvant chemotherapy (NCT) produces the same overall and disease-free survival rate as

adjuvant chemotherapy for ER^- tumors, with increased rates of BCS [17,31,32,49]. However, it is also well recognized that ER^+ tumors often respond poorly to NCT and therefore require robust alternatives [17,31,32,49]. Unfortunately, the adoption of neoadjuvant endocrine therapy (NET) for ER^+ tumors has been much slower. Three categories of NET are available: selective ER modulators (primarily tamoxifen), selective ER degraders (fulvestrant), and aromatase inhibitors (including letrozole, anastrozole, and exemestane) which block estrogen synthesis [26]. Historically, NET was reserved for patients who were considered too frail or unsuitable for surgery or chemotherapy; however, recent evidence is leading to the expansion of this treatment group [3, 28]. Three to 4 months of NET causes tumor shrinkage in two-thirds of patients and can convert up to 50% of mastectomy candidates into BCS candidates [38, 49]. Despite this, NET in breast cancer has been inadequately investigated and utilized compared to NCT, and the optimal duration of treatment remains unknown [8].

Patients with locally advanced breast cancer are frequently treated with preoperative (neoadjuvant) systemic therapy to downstage the tumor and improve surgical outcomes. The conventional approach has been to administer chemotherapy but for estrogen receptor–positive (ER+) tumors endocrine therapy is a logical alternative. Neoadjuvant endocrine therapy was initially investigated in older or medically frail individuals who were poor candidates for cytotoxic drugs. However, indirect comparisons suggest that preoperative endocrine therapy with an aromatase inhibitor promotes breast conservation probably as frequently as chemotherapy. As a result, primary systemic therapy with an aromatase inhibitor is now being explored in a younger, healthier population. A key advance would be the development of predictive biomarkers so that this treatment can be more confidently incorporated into routine clinical practice. Interestingly, it seems logical that such a test also would identify patients with highly endocrine therapy–responsive tumors that do not derive much benefit from adjuvant chemotherapy[18].

For patients with locally advanced breast cancer, neoadjuvant chemotherapy is commonly recommended to improve surgical outcomes. However, for postmenopausal women with oestrogen receptor (ER)-positive disease, endocrine treatment is a logical alternative because of its established efficacy in the adjuvant setting and the increasing recognition that chemotherapy may be less effective in ER+ HER2− disease Historically, neoadjuvant endocrine therapy was reserved for older and frail patients with ER+ breast cancer. However, recent studies of this treatment modality in younger and healthier postmenopausal women showed that the improved surgical outcomes and response observed with the endocrine approach do not show an interaction with age justifying the increased acceptance of neoadjuvant endocrine therapy in younger

postmenopausal women with better performance status. For premenopausal women, neoadjuvant endocrine therapy remains investigational. In this review, we will present results of the major neoadjuvant aromatase inhibitor (AI) trials and discuss recent progress in using neoadjuvant endocrine therapy as a research tool to assess endocrine responsiveness and evaluate novel therapeutic interventions. [38].

Neoadjuvant endocrine therapy: the clinical data

The potential benefit of endocrine therapy in the neoadjuvant setting was initially suggested in earlier studies of tamoxifen, as a primary treatment approach for elderly women with breast cancer who were too frail to undergo other forms of therapy such as surgery). The clinical response rate was in the range of 30% and higher, with long-lasting responses observed in some of these patients. Subsequent randomised trials of tamoxifen *vs* surgery followed by tamoxifen conducted in elderly women with operable breast cancer showed that surgery is essential for optimal local control, but tamoxifen alone achieved a similar overall survival compared with surgery followed by tamoxifen These investigations laid the foundation for the design of subsequent studies of AIs in younger and healthier postmenopausal women with bulky hormone receptor (HR)-positive disease to achieve better surgery outcome. The letrozole P024 trial the Immediate Preoperative Anastrozole, Tamoxifen or Combined with Tamoxifen (IMPACT) trial and the Preoperative 'Arimidex' Compared to Tamoxifen (PROACT) trial were three of these studies [16].

In the P024 trial, letrozole treatment was associated with a statistically significant improvement in the rate of breast conservation compared with tamoxifen. The anastrozole-based IMPACT and PROACT trials also showed a trend favouring the AI arm, although the results in comparison with tamoxifen were not statistically significant A meta-analysis of these trials supported the notion that an AI was more effective than tamoxifen for promoting breast conservation A promising 76% rate of breast conservation was also observed in a single arm phase II study of neoadjuvant exemestane in postmenopausal patients with HR+ tumours 3 cm or greater after 12 weeks of therapy The American College of Surgeons Oncology Group has recently completed accrual to the randomised phase III Z1031 trial to determine whether there are any differences in efficacy between the three approved AIs in this setting). Preliminary data from this trial indicate that there are no clinically significant differences between these agents as neoadjuvant treatment [23].

Preoperative endocrine therapy in premenopausal women

In an early study by Gazet , 13 premenopausal women with ER+ breast cancer received neoadjuvant goserelin, a gonadotropin-releasing hormone (GnRH) analogue. At 3 months, seven of the 13 women had an overall response by clinical assessment, suggesting that premenopausal women may also benefit from neoadjuvant endocrine manipulation investigated the use of letrozole and a GnRH analogue as primary therapy in premenopausal women with ER+ breast cancer. These patients received a GnRH analogue for a median of 5.2 months and letrozole for a median of 4 months. In the 32 evaluable patients, one achieved a pathological complete response (pCR) and 15 obtained a clinical and imaging partial response These studies suggest that neoadjuvant endocrine therapy is effective in selected premenopausal women with ER+ breast cancer and further study in this patient population is needed. [5].

Comparison with preoperative chemotherapy

A direct comparison between neoadjuvant chemotherapy and endocrine therapy was reported by Semiglazov et al (2007), in which 239 postmenopausal women with untreated invasive breast cancers that were ER and/or progesterone (PgR) positive received either combination chemotherapy with doxorubicin and paclitaxel every 3 weeks for four cycles (*n*=118) or AI treatment with either exemestane (*n*=60) or anastrozole (*n*=61) for 3 months). The clinical overall response, rates of pCR and disease progression did not differ significantly among the groups. The breast conservation rate was slightly higher in the AI groups at 33% compared with 24% in the chemotherapy arm. These findings support the hypothesis that AI therapy is an appropriate low toxicity neoadjuvant approach, but a definitive randomised study that compares neoadjuvant endocrine therapy to chemotherapy has yet to be reported. Ideally, a trial that compares the two approaches would take a predictive model forward into the clinical trial design, as subpopulations of breast cancer may benefit more from chemotherapy, while others from endocrine manipulation

Despite continuous scientific progress, patients diagnosed with locally advanced breast cancer (LABC)–here defined as stage IIB, IIIA, and IIIB cancer according to TNM classification [1], remain at high risk of recurrence and death from breast cancer (BC). Data from the surveillance epidemiology and end results (SEER) report five year survival rates of 70%, 52%, and 48% for patients presenting with stage IIB, IIIA, and IIIB disease respectively [33].

For these patients, current standard treatment is neoadjuvant chemotherapy (NCT) followed by surgery, adjuvant radiotherapy, and endocrine therapy to those with tumours expressing hormonal receptors. Phase III randomised trials showed that NCT is safe and at least equivalent to adjuvant chemotherapy in terms of disease-free and overall survival (OS) [34]. Furthermore, NCT induces tumour downstaging and increases rates of breast-conserving surgery (BCS) [13, 16]. However, factors other than tumour stage alone should be considered in the treatment plan of a patient with LABC, including 1) patient-related (age, global functional status, comorbidities, medications, social aspects, and patient preferences); 2) disease-related, in particular tumour biology–currently best defined as the molecular subtype of BC.

Luminal tumours, as defined by oestrogen receptor (ER) and/or progesterone receptor (PgR) expression by immunohistochemistry (IHC), account for 75% of all BC, summing up to 85% in women over 70 years old [18]. In this population, adjuvant endocrine therapy (AET) is likely to account for most of the gains obtained with the administration of adjuvant systemic treatment and the need for additional adjuvant chemotherapy in these patients remains debatable. In the Oxford meta-analysis, absolute OS benefits with polychemotherapy versus nil in postmenopausal women with HR+ disease are no higher than 3–4%, in contrast with more than 10% for the comparison of tamoxifen versus nil [9, 35]. Further support for this view is provided by recent studies of genetic signatures–in which the majority of women with luminal cancers have low-risk scores and do not derive meaningful benefit from the addition of chemotherapy to AET. These conclusions apply to both women with node negative [36, 42] and node positive disease [4]. Conversely, the majority of these patients will be exposed to significant and unnecessary chemotherapy-related toxicities, in particular the elderly and frail [5]. It is recognised that short and long term toxicity can become an issue especially in patients with an excellent prognosis–in particular the risk of myelodysplastic syndrome, non-lymphocytic leukaemia, and heart disease [6, 14].

The key role of AET in patients with luminal BC provides the main rationale for the investigation of NET in this population. Different groups have investigated the role of this treatment modality, in addition to biomarkers of response in this setting [20, 43]. In this review, we discuss the current role of NET and future perspectives in the field.

Primary endocrine therapy: to whom?

Endocrine therapy emerged in the early 1980s as a treatment option for elderly women who were unfit to be treated with chemotherapy or ineligible for surgery [37]. These studies were designed to evaluate the role of tamoxifen as a primary treatment option as an alternative to surgery rather than as a neoadjuvant treatment. Subsequently, trials

were designed to compare primary endocrine therapy (PET) with tamoxifen versus surgery (with or without AET) and a meta-analysis of seven clinical trials failed to show difference in OS (hazard ratio HR: 0.98; P = 0.9), but found that patients treated with surgery did experience gains in terms of progression-free survival (PFS) (HR: 0.55; P = 0.0006) [22]. However, an important limitation of these trials was the lack of ER status for the majority of the patients, as only one study selected patients according these biomarkers [23]. Based on these results, we recommend that PET should only be offered to women with HR+ tumours who are unfit for surgery or refuse this procedure, or to elderly women with short life expectancy as established by a qualified specialist and based on a validated geriatric assessment tool.

Conclusion.

Considering the existing data on NET discussed in this review and also given many uncertainties, one questions what is finally the right place of NET in current clinical practice? Probably the most suitable patients are postmenopausal women, in particular (but not limited to) older women, ideally with low-grade HR-rich (Allred ≥6 for both ER and PR) luminal A cancers. In addition, patient preferences, geriatric assessments, and comorbidities should all be taken into consideration to ensure that NET is the most suitable treatment in a particular situation. Additionally, because of their well-established role in predicting benefit from adjuvant endocrine therapy, genomic signatures can be occasionally used as a tool to gain deeper insights about tumour biology–a low risk result can boost confidence that NET is the right choice to a given patient.

Abbreviations

*ER:*Estrogen receptor

*PgR:*Progesterone receptor

*LABC:*Locally advanced breast cancer

*BCS:*Breast-conserving surgery

*NET:*Neoadjuvant endocrine therapy

*NCT:*Neoadjuvant chemotherapy