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# THE CHOICE OF CHEMOTHERAPEUTIC TREATMENT OF BREAST CANCER (TAKING INTO ACCOUNT THE BIOLOGICAL SUBTYPES IN OLDER WOMEN)

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**SUMMARY**
Patients with the hormone-sensitive and Her2neu amplified tumor subtype have a better short-term prognosis than patients with the hormone-negative and Erb-B2 overexpressing subtype. With triple-negative breast cancer, chemotherapy is the only systemic therapy that is beneficial, and should be used in patients who are in good physical shape.

**KEYWORDS:** breast cancer, targeted and systemic chemotherapy, luminal A subtype, luminal B subtype, HER2 protein.

Breast cancer (BC) is the most common malignant neoplasm and ranks first among all malignant tumors in women. Despite the fact that the prevalence of the tumor process is the most important criterion for the prognosis and choice of treatment tactics, it does not always reveal its correlation with the effectiveness of treatment and the outcome of the disease. Recently, a number of molecular markers of tumor cells have been included in the list of prediction criteria.[5,16,18] Among patients 65 years and older, most tumors are characterized by positive expression of steroid hormones receptors (ER +) and HER2 negative (HER2-) status - these are luminal A subtype tumors, which are characterized by a favorable clinical course and outcome, a later age of occurrence, a high degree of differentiation, low Ki67 proliferative index, a relatively favorable prognosis in comparison with hormone-negative tumors. Also, this type is characterized by a low rate of relapse and a longer life span.[4.20] It responds well to hormone treatment in both the neoadjuvant and adjuvant regimen and, as a rule, to neoadjuvant chemotherapy. As you know, the luminal A subtype is characterized by low proliferative activity, and as a result, low sensitivity to adjuvant chemotherapy, so the main methods of treatment are the surgical method, hormone therapy with or without radiation therapy. Various studies among patients over 70 years old with hormone-sensitive tumors have shown that Tamoxifen reduces the annual risk of breast cancer recurrence by about 2 times and the annual probability of death from breast cancer by 37%, regardless of the state of the lymph nodes. Tamoxifen is well tolerated by elderly patients and is available due to its low cost. It can also maintain or increase bone density and lower cholesterol in postmenopausal women.[6] However, there is an approximately 1% risk of endometrial cancer and venous thrombosis with 5 years of use. Among elderly patients, recommendations to conduct an annual examination of the pelvis and take a Pap smear may have some difficulties. A number of large clinical trials have been conducted that compared Tamoxifen and aromatase inhibitors (AI), and found a slight advantage in the relapse rate in the AI group. However, in terms of overall survival compared with Tamoxifen, the benefits are negligible. Although there are many strategies for endocrine therapy, the use of Tamoxifen and a switch after 3 years to aromatase inhibitors showed an increase in survival of about 1% and represents the best strategy.[6,23]

Luminal B subtype is hormone-sensitive, it is aggressive in comparison with the Luminal A subtype, it is characterized by low differentiation, high proliferative index Ki67%, large tumor size, involvement of lymph nodes, an earlier age of occurrence. Up to 20% of breast cancers occur after 65 years. It has a worse prognosis and a greater likelihood of relapse in comparison with Luminal A. In Her2, amplification (up to 10% of tumors) may be insensitive to hormone therapy, in contrast to the trastuzumab targeted therapy.[10,19] In addition to the possible overexpression of Her2neu with the Luminal B subtype, a high degree of histological malignancy G3 is also observed. Endocrine therapy is the basis for adjuvant treatment of elderly patients with luminal B breast cancer subtype. The main problem in the treatment

of the elderly with the Luminal B subtype is the determination of which of them chemotherapy will potentially bring more benefits. For patients with T1 and T2 and the absence of lymph node damage, hormone-sensitive tumors undergoing adjuvant endocrine therapy, the value of chemotherapy can be determined using prognostic tests such as Oncotype DX, MammaPrint, etc.[14,22] This analysis contains information that the maximum benefit of chemotherapy in this group is observed among patients with high risk of relapse, and the minimum benefit among patients with low risk of relapse, including women with 1-3 affected lymph nodes.[2,11,21] The authors suggest that for patients with a moderate risk of relapse, the value of chemotherapy for reducing breast cancer mortality can be evaluated using www.adjuvantonline.com. The value of chemotherapy for the elderly with T1 and T2 tumors without affection of the lymph nodes with low risk of relapse is also evaluated in randomized clinical trials. A similar study is carried out for patients with 1-3 affected lymph nodes. The 13th International Conference on Breast Cancer in St.Gallen recommended the use of taxanes and anthracyclines for the luminal B subtype, despite the fact that it could not determine the preferred chemotherapy regimen.[1]

The decision to use chemotherapy and trastuzumab in the elderly should be individual, especially for patients who are in poor physical shape. In most cases, the addition of trastuzumab to chemotherapy improved survival compared to chemotherapy alone. Elderly patients showed good tolerability of trastuzumab, but careful observation is necessary. As age increases, there is an increasing risk that trastuzumab can cause heart failure. Patients with heart disease and diabetes with a high degree of risk may be exposed to the development of cardiotoxicity, and the increased risk may be associated more with the prevalence of comorbidity than with age.[17] The advent of new targeted drugs, for example, Lapatinib, Neratinib, with a smaller molecule directed against HER2neu receptors, can also increase the therapeutic effect and reduce side effects when added to chemotherapy in elderly patients. Erb-B2 overexpressing subtype is hormone-negative, characterized by a high proliferative index Ki67%, low differentiation, large tumor size, involvement of lymph nodes, and a high probability of a negative outcome of the disease.[7] It is very difficult to decide on chemotherapy for an older woman. This decision should be preceded by a consideration of the effect of this treatment on improving survival, and a study of potential toxicity that could result in loss of functionality and a decrease in quality of life. After deciding on the appointment of chemotherapy, the oncologist faces a second difficult choice - which chemotherapy regimen to choose. Adjuvant! Online directly compares survival with different chemotherapy regimens. He divides the regimes into the first, second and third (most aggressive), given the benefits of treatment. The second-generation regimen, consisting of 4 cycles of TC, more effective than 4 cycles of AC, was evaluated in a large number of elderly patients and showed overall good tolerance. For patients in good shape with a high risk of relapse, treatment with the third-generation regimen improves survival by several percent compared with the regimes of the first and second generation.[9,10] For patients at low risk of relapse, the authors suggest considering a second-generation regimen such as TC to avoid potential anthracycline cardiac and hematologic toxicity. For high-risk patients, it is necessary to consider a third-generation regimen if, according to estimates, there is an improvement in 5-year survival by several percent. Anthracycline- and taxane-containing modes of the third generation should be applied to patients with high functionality and minimal concomitant diseases.

The HER2 protein is a unique and useful target for drug treatment. It occurs in 15-25% of all cases of breast cancer, but with age these indicators are much lower. Patients with HER2 positive tumors benefit most from the combination of chemotherapy and trastuzumab. Due to the fact that cardiac toxicity is a major side effect of trastuzumab and the incidence of heart disease increases with age, elderly patients are at risk for cardiac toxicity and require close monitoring. Measurement of the ejection fraction of the left ventricle before therapy and every 2 months during treatment should be the norm. The combination of trastuzumab regimen with docetaxel, carboplatin and trastuzumab is similar in effectiveness to trastuzumab and anthracycline-containing chemotherapy, but it is associated with less cardiac toxicity and is highly recommended for the treatment of elderly patients.[8]

Most patients with thrice-negative breast cancer in comparison with other biological subtypes recur much earlier (usually within 5 years), and also have significantly worse survival. The basal-like subtype is the most aggressive type of tumor; about 15% of cases occur.[13] An earlier age of occurrence in comparison with other subtypes is noted, low differentiation, high proliferative index Ki67%, relatively large tumor size, involvement of lymph nodes, nuclear pleomorphism, necrosis, and a high probability of the development of locally common and metastatic forms. In a retrospective study, CancerandLeukaemiaGroup B (CALGB) found that older and younger patients had a similar decrease in breast cancer mortality and relapses during chemotherapy containing a greater number of cytostatics, or higher doses of agents. This large retrospective estimate of nearly 6,500 patients provides evidence that age should not be an obstacle to intensive chemotherapy regimens if patients are in good health.[13,15] The EBCTCG meta-analysis also showed that chemotherapy in general is as effective in patients older than 65 as in younger women. The toxicity of chemotherapy compared with endocrine therapy is much higher and can lead to a decrease in physical activity and quality of life. Palliative measures without chemotherapy may be the smart choice for debilitated elderly patients.[3,8] The specific choice of chemotherapy regimen depends on several factors, the

individual characteristics of the patient, doctor and patient preferences and the availability of drugs. Sequential treatment with a single cytostatic agent may be more preferred for elderly debilitated patients, given the potential reduction in toxicity risk. However, the CALGB 49907 study showed lower results with monochemotherapy in the elderly compared with combined regimens. Two retrospective SEER studies have shown that adjuvant chemotherapy improves overall survival in elderly patients ≥70 years of age with a hormone-negative subtype. A prospective randomized study by CALGB found that standard chemotherapy for CMF or AC was superior to using capecitabine as adjuvant chemotherapy for elderly patients ≥ 65 years of age with breast cancer at an early stage.[13,18] The most significant effect was in hormone-negative subtypes. Despite the fact that they achieved a reduction in toxicity compared with standard therapy, relapse-free and overall survival was higher in the standard chemotherapy group. After three phases of research involving 510 patients with stage I-III breast cancer, Jones S. et al. compared the efficacy of TC against AC in a subgroup analysis of elderly ≥ 65 years of age and young women. It was found that TC is associated with more favorable disease-free and overall survival than AC in both age groups, including patients with hormone-negative or Her2-negative tumors.[12] TC chemotherapy is well tolerated with low neutropenia (about 8%) in elderly patients. Some studies have shown that at high rates of development of febrile neutropenia with chemotherapy according to the TC scheme, the prophylactic use of granulocyte colony-stimulating factor is possible, as was proposed by the European Organization for the Study and Treatment of Cancer in 2011, but not in all cases.[8] These data confirm that elderly safe patients with triple negative breast cancer have indications for treatment with the most modern chemotherapy regimens.

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