K., Dubruc E.P.L. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. N Engl J Med. 2020. vol.382. no.18. P. 1708-1720.

12.Patane L. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019-positive mothers and neonates at birth. Am J Obstet Gyncol MFM. 2020. vol. 2. P.100-145.

13.Penfield C.A. Detection of severe acute respiratory syndrome coronavirus 2 in placental and fetal membrane samples. Am J Obstet Gynecol MFM. 2020. Vol. 2. P. 100-133.

PRESCRIBING HORMONE THERAPY FOR BREAST CANCER: A PERSONALIZED APPROACH BASED ON BIOLOGICAL SUBTYPES

Alimkhodjayeva L.T., Yuldashev R.R.
Republican Specialized Scientific and
Practical Medical Center of Oncology and Radiology
Tashkent, Uzbekistan

НАЗНАЧЕНИЕ ГОРМОНАЛЬНОЙ ТЕРАПИИ ПРИ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ: ПЕРСОНАЛИЗИРОВАННЫЙ ПОДХОД НА ОСНОВЕ БИОЛОГИЧЕСКИХ ПОДТИПОВ

Л.Т. Алимходжаева, Р.Р. Юлдашев
Республиканский специализированный научно-практический
медицинский центр онкологии и радиологии
Ташкент, Узбекистан
DOI: 10.31618/ESU.2413-9335.2022.4.94.1601

ABSTRACT

Patients with hormone-sensitive and Her2neu amplified tumor subtypes have a better short-term prognosis than patients with hormone-negative and Erb-B2 over expressing subtypes. At the hormone-positive luminal A subtype of breast cancer, hormone therapy is the only systemic therapy that is beneficial and should be used in patients who are in good physical shape..

РЕЗЮМЕ

Пациенты с гормоночувствительными и амплифицированными подтипами опухоли Her2neu имеют лучший краткосрочный прогноз, чем пациенты с гормонотрицательными и сверхэкспрессирующими подтипами Erb-B2. При гормонопозитивном люминальном А подтипе рака молочной железы гормональная терапия является единственной эффективной системной терапией, которую следует применять у пациенток, находящихся в хорошей физической форме.

Key words: breast cancer, target and system chemotherapy, luminal A type, luminal B type, protein HER2.

Ключевые слова: рак молочной железы, таргетная и системная химиотерапия, люминальный тип А, люминальный тип В, белок HER2.

Breast cancer (BC) is the most common malignant neoplasm and takes the first place among all malignant tumors in women. Despite the fact that the prevalence of the tumor process is the most important criterion for prognosis and choice of treatment tactics, its correlation with the efficiency of treatment and the outcome of the disease is not always revealed. A number of molecular markers of tumor cells have been included in the list of prognosis criteria recently [1-3]. Among patients of 65 years and older, most tumors are characterized by positive expression of steroid hormone receptors (ER+) and HER2 negative (HER2-) status – these are tumors of the luminal A subtype, which are characterized as follows: favorable clinical course and outcome, later age of occurrence, high degree of differentiation, low proliferative index Ki67, relatively favorable prognosis in comparison with hormone-negative tumors. Also, this type is characterized by a low relapse rate and a long life expectancy [4-5]. It responds well to hormone treatment both in neoadjuvant and adjuvant regimen, and as a rule, to neoadjuvant chemotherapy. As it is known, the luminal A subtype is characterized by low proliferative activity, and as a consequence, low sensitivity to adjuvant chemotherapy. Therefore, the main methods of treatment are surgical method, hormone therapy with or without radiation therapy.

Various studies among patients over 70 years 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 condition of the lymph nodes. Tamoxifen is well tolerated by elderly patients and is available because of the low price. It can also maintain or increase bone density and lower cholesterol levels in postmenopausal women [6]. However, there is an approximately 1% risk of endometrial cancer and venous thrombosis at 5 years of use. Recommendations to conduct an annual pelvic examination and take a Pap smear may have some difficulties among elderly patients. There have been a number of large clinical trials comparing Tamoxifen and aromatase inhibitors (AI) and a slight advantage in the recurrence rate in the IA group has been found. However, in terms of overall survival in compare with Tamoxifen, the benefits are negligible. Despite the presence of many strategies regarding endocrine therapy, the use of Tamoxifen and the transition to aromatase inhibitors after 3 years showed an increase

in survival by about 1% and represents the best strategy [6-7].

The luminal B subtype is hormone-sensitive, characterized by aggressiveness in comparison with the luminal A subtype. It is characterized by low differentiation, high proliferative index Ki67%, large tumor size, involvement of lymph nodes, and earlier age of onset. Up to 20% of breast cancer cases occur after the age of 65. It has a worse prognosis and a greater probability of relapses compared to luminal A. With Her2 amplification (up to 10% of tumors), it may be insensitive to hormone therapy, unlike targeted therapy with Trastuzumab [8-9]. In addition to the possible over expression of Her2 neu at the luminal subtype, a high degree of histological malignancy of G3 is also observed. Endocrine therapy is the basis of adjuvant treatment of elderly patients with luminal B subtype of breast cancer. The main problem in the treatment of elderly patients with luminal B subtype is to determine for which of them chemotherapy will potentially bring more benefits.

For patients with T1 and T2 and the absence of lymph node lesions, hormone-sensitive tumors undergoing adjuvant endocrine therapy, the value of chemotherapy can be determined using prognostic tests such as Oncotype DX, MammaPrint, etc. [10-11]. This analysis contains information that the maximum benefit from 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 [12-14]. The authors believe that for patients with an average risk of recurrence, the value of chemotherapy to reduce breast cancer mortality can be assessed using the website www.adjuvantonline.com The value of chemotherapy for elderly patients with T1 and T2 tumors without lymph node lesion with low risk of recurrence is also evaluated in randomized clinical studies. A similar study is carried out in patients with 1-3 affected lymph nodes. The 13th International Breast Cancer Conference in St.Gallen recommended the use of taxanes and anthracyclines in the luminal B subtype, despite the fact that it was not able to determine the preferred chemotherapy regimen [15].

The decision on the use of chemotherapy and trastuzumab in elderly patients should be individual, especially for those who are in poor physical shape. In majority of cases adding trastuzumab to chemotherapy improved survival in compare with chemotherapy alone. Elderly patients have shown trastuzumab to be well tolerated, but careful monitoring is required. As the age increases, there is an increasing risk that trastuzumab may cause heart failure. Patients with high-risk heart disease and diabetes may be at risk of developing cardiotoxicity, and the increased risk may be more related to the prevalence of comorbidity rather than age [16]. The emergence 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, high probability of a negative outcome of the disease [17]. It is very difficult to make a decision about prescribing chemotherapy to an elderly woman. This decision should be preceded by a review of the effect of this treatment on improving survival, and the study of potential toxicity which can lead to loss of functionality and a decrease in quality of life. After deciding on the prescribing of chemotherapy, the oncologist faces a second difficult choice - which chemotherapy regimen to choose. AdjuvantOnline directly compares survival rates with different chemotherapy regimens. He divides the regimens into the first, second and third (the most aggressive), taking into account the benefits of treatment. The second-generation regimen consisting of 4 TC cycles, more effective than 4 AC cycles, was evaluated on a large number of elderly patients and showed overall good tolerability. For patients in good shape with a high risk of relapse, treatment with the third-generation regimen improves survival by several percent in compare with the first and second-generation regimens [18,8]. For patients with a low risk of relapse, the authors suggest considering a second-generation regimen, such as TC, to avoid potential anthracycline cardiac and hematological toxicity. For patients at high risk, a third-generation regimen should be considered if a few percent improvements in 5-year survival are estimated. Anthracycline- and taxane containing third-generation regimens should be used in 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 breast cancer cases, but with age these indicators become much lower. Patients with HER2-positive tumors benefit most from a combination of chemotherapy and trastuzumab. Due to the fact that cardiac toxicity is the main side effect of trastuzumab, and the incidence of heart disease increases with age, elderly patients are at risk for cardiac toxicity and require careful monitoring. Measurement of the left ventricular ejection fraction before the start of therapy and every 2 months during treatment should become the norm. The combination of trastuzumab regimens with docetaxel, carboplatin and trastuzumab is similar in efficiency with trastuzumab and anthracycline-containing chemotherapy, but is associated with lower cardiac toxicity and is strongly recommended for the treatment of elderly patients [19].

The majority of patients with triple negative breast cancer relapse much earlier (usually within 5 years) in comparison with other biological subtypes, and also have significantly worse survival. The basal-like subtype is the most aggressive type of tumor, occurring in about 15% of cases [20]. There is an earlier age of occurrence in comparison with other subtypes, low differentiation, high proliferative index Ki67%, relatively large tumor size, involvement of lymph nodes, nuclear pleomorphism, necrosis, and a high probability of locally widespread and metastatic forms. In a retrospective study of Cancer and Leukaemia Group B (CALGB), it was found that elderly and young patients had a similar decrease in mortality from breast cancer and relapses during chemotherapy containing a

larger number of cytostatics or higher doses of agents. This large retrospective assessment of almost 6,500 patients contains evidence that age should not be an obstacle to intensive chemotherapy regimens if patients are in good health [20-21]. The EBCTCG meta-analysis also showed that chemotherapy in general has the same efficiency in patients over 65 years as in younger women. The toxicity of chemotherapy in compare with endocrine therapy is much higher and can lead to a decrease in physical activity and life quality. Palliative measures without chemotherapy may be a reasonable choice for weakened elderly patients [22,19].

The specific choice of chemotherapy regimen depends on several factors: the individual characteristics of the patient, the doctor and the patient's preferences and the availability of medicines. Sequential treatment with a single cytostatic agent may be more preferable for elderly debilitated patients taking into account the potential reduction of toxicity risk. However, the CALGB 49907 study showed lower results at monochemotherapy in elderly patients compared with combined regimens. Two retrospective SEER studies have shown that adjuvant chemotherapy improves overall survival in elderly patients aged ≥ 70 years with a hormone-negative subtype. A prospective, randomized trial by CALGB found that standard CMF or AC chemotherapy was superior to the use of capecitabine as adjuvant chemotherapy in elderly people at the age ≥ 65 years with early-stage breast cancer. [13,18]. The most significant effect was in hormone-negative subtypes. Despite the fact that they achieved a reduction in toxicity in compare with standard therapy, relapse-free and overall survival was higher in the standard chemotherapy group.

After three phases of studies involving 510 patients with stage I-III breast cancer, Jones S. et al. compared the efficacy of TC against AC in a subgroup analysis in elderly people at the age ≥ 65 years and younger women. It was found that TC is associated with more favorable relapse-free and overall survival than AC in both age groups, including patients with hormone-negative or Her2-negative tumors [23]. Chemotherapy according to the TC scheme is well tolerated with a low level of neutropenia (about 8%) in elderly patients. Some studies have shown that at high rates of febrile neutropenia development at chemotherapy according to the TC scheme, the preventive use of granulocyte colony-stimulating factor is possible, as proposed by the European Organization for Cancer Research and Treatment in 2011, but not in all cases [19]. These data confirm that elderly healthy patients with triple-negative breast cancer have indications for treatment with the most modern chemotherapy regimens.

References

1.Diab S.G. Tumor characteristics and clinical outcome of elderly women with breast cancer. /Elledge R.M, Clark G.M. //JNatlCancerInst 2000. –V. 92. –P 550–556

2.RudenstamC . Randomized trial comparing axillary clearance versus no axillary clearance inolder patients with breast cancer: first results of International Breast Cancer Study Group. Trial 10-93. /Zahrieh D. // J ClinOncol 2006. –V.24. –P.337–344

3.Schrag D. Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 or BRCA2 mutations. / Kuntz K, Garber J. // JAMA 2000.-V.283. –P.617–624

4.Christman K. Chemotherapy of metastatic breast cancer in the elderly. / Muss H.B, Case L.D. //ThePiedmontOncologyAssociationexperience. JAMA 2012.-V. 268.-P 57–62

5.Slamon D. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. / Leyland-Jones B, Shak S. NEnglJMed 2001. –V.344.-P. 783–792

6.Dowsett M. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: aTransATAC study. /Cuzick J, Wale C.// JClinOncol 2010.-V.28.-P 1829–1834

7.Semiglazov V.F. Breast cancer. Biology, local and systemic treatment. In Russian/Semiglazov V.V. // SIMK 2014. N.1. P- 298-341

8.Gregor M. Trastuzumab-related cardiotoxicity among older breast cancer patients. /Zhang N, Niu J. //ASCO Meeting Abstract. JClinOncol 2012.-V.30. -P 135

9.Slamon D. Adjuvant Trastuzumab in HER2-Positive Breast Cancer. // Eiermann W, Robert N. // NEnglJMed 2011.-V. 365.-P. 1273–83

10.Partridge A. Adherence and persistence with oral adjuvant chemotherapy in older women with early-stage breast cancer in CALGB 49907: adherence companion study 60104. / Archer L, Kornblith A. // JClinOncol 2010. –V. 28.-P. 2418–2422

11.Jones S. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US oncology research trial 9735. / Holmes F, O'Shaughnessy J. // JClinOncol 2009. –V. 27. – P 1177–1183

12.Albain K. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. /Anderson S, Arriagada R.// Lancet 2012. -V.379.-P 432–444

13.Jones S. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US oncology research trial 9735. / Holmes F, O'Shaughnessy J. // JClinOncol 2009. –V. 27. – P 1177–1183

14.Wildiers H. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. / Kunkler I, Biganzoli L. // LancetOncol 2007. –V.8.-P.1101–1115

15.Abe O. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. / Abe R, Enomoto K.// Lancet 2005. –V.365. –P 1687–1717

16.Sawaki M. Safety of adjuvant trastuzumab for HER - 2- overexpressing elderly breast cancer patients: a multicenter cohort study. / Mukai H, Tokudome N. // Breast Cancer 2012. –V.19.-P. 253–258

17.Foulkes W. Triple-negativebreastcancer. /Smith I, Reis J.// NEnglJMed 2010.-V.363.-P 1938–1948

18.Geyer C. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. /Forster J, Lindquist D. //NEnglJMed 2006.-V.355.-P 2733–2743

19.Freyer G. Adjuvant docetaxel/cyclophosphamide in breast cancer patients over the age of 70: results of an observational study. /Campone M, Peron J.// CritRevOncolHematol 2011.-V.80.-P 466–473

20.Paik S. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. / Tang G, Shak S. // JClinOncol 2006. –V.24.-P 3726–3734

21.Ravdin P. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. / Siminoff L, Davis G. // JClinOncol 2001. –V.19. –P. 980–991

22.Burstein H J. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. / PrestrudA.A, Seidenfeld J.// J Clin.Oncol 2010.-V. 28.-P 3784–3796

23.Muss H. Investigators. Adjuvant chemotherapy in older women with early-stage breast cancer. /Berry D, Cirrincione C.// NEnglJMed 2010. –V. 360.-P 2055–2065