MODERN PRINCIPLES OF ADJUVANT TREATMENT OF BREAST CANCER

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Summary. Breast cancer takes first place among all cancers in women. One of the main methods of treatment of this cancer is the chemotherapy. The use of adjuvant chemotherapy and hormonal therapy significantly improves outcomes in patients, and 5-year disease-free survival rate is 98% in the favorable prognosis groups. This article presents the principles of choice of adjuvant therapy in the treatment of patients with breast cancer.

Key words: breast cancer, adjuvant chemotherapy, hormone therapy

Choice of effective breast cancer (BC) treatment is one of the most complicated medico-social problems in modern oncology. BC takes leading place in morbidity and mortality rates among all malignant tumors in female. Its relative density is about 20 % [1, 2]. Annually more 1 mln of females are registered with firstly diagnosed BC. More 600 thousands of patients die [3]. Similar tendency is observed in the Europe [4]. BC is the most widespread cancer type among female population in Ukraine [5]. By the data of National Cancer register [2] 17410 patients were registered with newly diagnosed BC in 2010, that is 19.3 % of all cases of newly diagnosed malignant tumors in females. 7969 patients died, that cover 16.5 % of all cancer deaths.

The highest mortality rate is registered in the age of 40-50 years old. Important is that the pic of morbidity is registered in the age group of 45–60 years old. Thereby woman in able-bodied age fall ill and die of BC more often. At the same moment the morbidity of other cancer types increase at the age 70–80 years old. The morbidity risk after 65 years old is 5.8 times higher, and almost 150 times higher then in the age younger 30 years old.

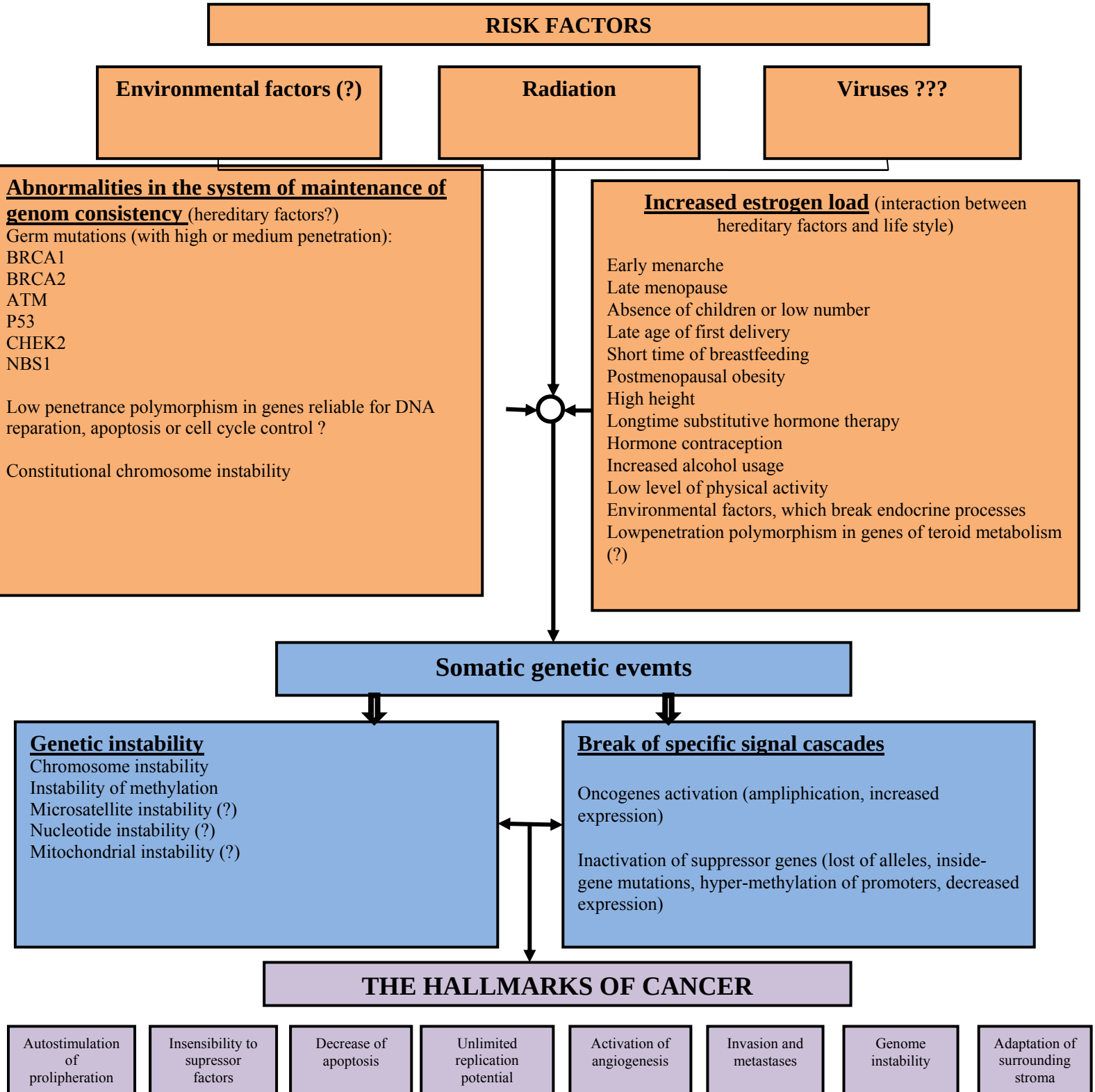
Specialty of disease course and biological features of BC cause usage of all treatment methods (surgical, radio-, chemo-, hormonotherapy) at proper phases of

therapy. Optimal sequence of their application is still the subject of active clinical trials.

Accept the age few dozen of factors which influence to the treatment strategy described in the literature. These factors come to two molecular-biological categories: increase exposition of androgens and deficiency of facilities of genome stability support [6].

Modern conception of the role of risk factors in pathogenesis of BC described at the Figure [7].

Figure. Risk factors and molecular pathogenesis of breast cancer



More then 10 years ago proliferative effect of estrogens on the breast epithelium was described. But only recently it became known that it's not sole mechanism of their influence. Some estrogen metabolites may directly cause the damage of cell DNA. In some cases estrogen overload (early menarche or late menopause) partially may be explained by genetic instability. However usual source of hyperestogenity are factors connected with modern lifestyle: low number or absence of deliveries, limited time of breastfeeding, late first delivery, overeating, and insufficient physical activity and so on. Unfavorable influence of oral contraceptives and substitutive hormone therapy was confirmed repeatedly, but final opinion on this didn't know [7]. The role of other exogenic endocrine factors is studying at the moment [8, 9]. There weren't detected any environmental cancerogenes clearly connected to the BC contrary to the lung and urinary bladder cancer. Connection of food additives and BC risk was unconvincing also [7]. Some investigators revealed the connection between multiple breast traumas and following BC development [10]. The role of viruses studied many years, but there isn't sole opinion in the question [11].

Second category of molecular-biological factors of BC risk is the group of factors, which cause the deficiency of facilities of genome stability support. There are two lines of arguments. First, the known genes of predisposition to BC which are involved to the cell DNA damage recognize and repair. Second, the convincing results of studies showed the connection between BC risk and constitutional chromosome instability [7, 12, 13].

The most important genes of BC predisposition are BRCA1 (number in GenBank NM-007294) and BRCA2 (number in GenBank NM-000059). These genes play key role in the DNA reparation, cell cycle regulation and chromatin remodellation [7]. They cause about 20 % of inherited BC [7, 14]. Investigation of families with inherited BC showed fatal risk of BC development in bearers of the BRCA gene mutation. From other side, among random sample of BC patients in the

age younger 70 years old penetrance of C BRCA1 gene is 65 % and only 45 % for BRCA2 [15].

In definite terms genes ATM, p53, PTEN, inherited mutations, which predispose to ataxia-teleangiextasy, Li-Fraumeni or Couden syndrome, may be also connected with predisposition to BC. Increase of BC rates was observed among bearers of these genes [7, 16]. BC occur mostly didn't connected with inheritance of germinal mutations. Though, epidemiological data indicate obvious presense of genetic component in pathogenesis of sporadic BC [7].

Unsatisfied results of only surgery treatment in patients with BC (in advanced and overadvanced variants distant metastases are observed in 70-80 % of patients) pushed investigators for search of additional systemic treatment methods, e.g. chemotherapy (CT) and hormonotherapy.

Disease course and treatment efficacy of BC determined by biological features of tumor cells – presence of steroid hormones receptors (estrogen, progesterone), Her-2/neu level of expression, malignancy grade (G), spread of the disease, patients' age and ovarian function.

Modern conception of disease prognosis and treatment methods assessed by biological features of tumor: 1) patients with hormonosensitive tumors positive by estrogen (ER) or progesterone (PR) receptors; 2) patients with hyperexpression of Her-2/neu; and 3) patients with "triple-negative" BC (negative by ER, PR and level of Her-2/neu) [17]. Patients with hormonosensitive tumors have the most favorable prognosis. In this group combination of radical breast saving operations followed by adjuvant CT with minimal toxicity provide good treatment results.

BC is hormonosensitive tumor; thereby hormonotherapy is one of the most important treatment methods.

Hormonotherapy is widely used in the treatment of hormonosensitive BC at present time. Despite of different mechanisms of action, role of known methods of hormonotherapy come to decrease of influence of estrogens on tumor cells, that determine reduction of tumor growth, and in some patients – decrease of tumor mass, even its full disappearance [17]. It may be reached in premenopausal patients with ovarioectomy or ovarian irradiation, or by usage of superagonists of luteinized

hormone realizing hormone (LH-RH). Such chemical castration has reversible character. Goserelin (Zoladex) or leiprorelin (Prostap) are used.

During the treatment of hormonosensitive BC agonists of gonadotropic hormones of hypophysis (goserelin), drugs from antiestrogen group - selective modulators of ER (tamoxifen, torimefen) and inactivator of ER (fulvestrant), selective aromatase inhibitors – nonsteroid (letrozole and anastrozole) and steroid (exemestane) are used. Popular earlier progestins take modest place, androgens and estrogens are used very rare. Possibility of prescribing drugs from antiprogesterone groups (miphepristone, onaprestone) and antianrogens (bicalutamide) are under observation.

Direct correlation between presence and level of expression of steroid hormones receptors and hormonotherapy efficacy was observed. Treatment efficacy in patients with ER+ BC is 50-60 % and ER- BC only 5-10 %. About 30 % patients with uncertain receptor status show positive response to the hormonotherapy.

Hyperexpression and/or amplification of HER-2/neu gene in BC cells belong to the most unfavorable prognostic factors. It associated with aggressive morpho-functional parameters of tumor cells. Treatment results in this group of patients are unsatisfied. Relapsed-free (RFS) and overall survival (OS) are much worse compared to hormonosensitive BC, efficacy of cytotoxic treatment is the lowest.

Presence of hormone receptors is the most important factor that predicts tumor susceptibility to the hormonotherapy. Absence of hormone receptors predicts tumor susceptibility to the CT [18-21]. Though, this doesn’t mean that CT shouldn’t be performed in patients with positive ER and/or PR.

Analysis of publications showed that adjuvant CT seriously improve rates of RFS on 23.8 % and decrease death rate on 15 %. Especially it was significant in patients younger 50 years old (on 34 % and 27 % respectively) [22].

Efficacy of adjuvant CT depends on biological features of tumor. Tumors with high level of expression of ER, PR and low level of expression of HER-2/neu have as a rule low malignancy grade and cell proliferation rate and, by results of multigenic analysis, low relapse scale. Retrospective studies showed that combination of adjuvant CT and hormonotherapy in patients with “triple-negative” BC didn’t

improve treatment results [23-25]. Contrary, patients with absence or low expression of hormone receptors, but high expression of HER-2/neu, and patients with high malignant grade or proliferation rate, have high relapse scale, resistance to hormonotherapy, but sensitiveness to CT; patients with HER2/neu+ tumors are sensitive to adjuvant trastuzumab therapy.

Analysis of adjuvant hormonotherapy and CT efficacy in BC patients confirmed the suspicion that increase of the role of one these treatment methods decrease the role of another. Recent clinical trials showed that adjuvant hormonotherapy and CT prescribing should be based on biological and patho-morphological features of tumor (Table 1).

Table 1. Adjuvant treatment of HER2/neu – BC (ASCO-2010).

BC subtype	Risk factors of relapse	Adjuvant hormonotherapy	Adjuvant chemotherapy
Triple-negative BC	Any stage	Not applicable	Antracycline and taxan
Receptor positive BC (ER+ and/or PR+)	Low risk: 1. High level of expression of ER and PR 2. Low malignancy grade 3. Limited number of involved Lymph nodes (0-3) 4. Absance or limited invasion in lymphatic vessels (LVI) 5. Low tumor size (≤2 cm) 6. Low relapse scale (RS)	Postmenopause: Tamoxifen ± aromatase inhibitors *vs* aromatase inhibitors Premenopause: Tamoxifen ± ovarial supression	–
	1. High risk: Low level of ER and/or PR 2. High malignancy rate 3. High number of involved Lymph nodes (4 and more) 4. Spread	Postmenopause: Tamoxifen ± aromatase inhibitors *vs* aromatase inhibitors Premenopause: Tamoxifen ± ovarial supression	Antracycline and taxan

	invasion in lymphatic vessels (LVI) 5. Low tumor size (5 cm and more) 6. Higher relapse scale (RS)		

BC tumors are sensitive to majority of modern anticancer drugs, especially to doxorubicin (40 % efficacy, similar to epirubicin and mitoxantrone), cyclophosphamide (35 % efficacy), metotrexate (35 % efficacy), fluorouracil and tegafur (25 % efficacy).

Standard and the most effective regimens of adjuvant CT are antracycline-based regimens FAC (cyclophosphamide, doxorubicin, 5-fluorouracil) and FEC (cyclophosphamide, epidoxorubicin, 5-fluorouracil). Optimal number of treatment cycles in adjuvant regimen is 6 cycles. This scheme allows achieve better distant results compared with 3 cycles [25].

Two randomized trials studied role of paclitaxel in adjuvant CT in patients with BC after few cycles of antracycline-based regimens [26, 27]. Trials didn't show the improvement of distant results of paclitaxel addition except patients with "triple-negative" BC.

Targeted drug trastuzumab (humanized monoclonal antibody (MCAB) epidermal growth factor to (EGFR) - HER-2/neu) is effective in patients with HER-2/neu Hyperexpression. Trastuzumab improves RFS and OS in combination with adjuvant CT in patients with operable BC [28-30]. Metaanalysis showed significant decrease of relapses rate and distant metastasis in the group of patients, which received trastuzumab compared with the group of CT alone [31].

Operable patients with BC need additional adjuvant CT for improvement of treatment results. The only exception is small group of patients with favorable prognosis older 35 years old with highly differentiated (G1) hormonosensitive (ER+, PR+) tumor with size lower 1 cm without metastases (stage T1aN0M0).

The most important prognostic factors are presence and number of involved lymph nodes, size of primary tumor, differential grade, age, menstrual function, level offer and/or PR, Hyperexpression of (Table 2).

Table 2. Prognostic groups in patients with BC without metastases in regional lymph nodes.

Prognostic group	Characteristic
Low risk (in case of presence of all characteristic)	ER + and/or PR + Malignancy grade I (G I) Age > 35 years old
High risk (in case of presence of one or more factors)	ER − PR − pT > 2 cm Malignancy grade II−III (G II−III) Age < 35 years old

Annotation: ER – estrogen receptors; PR – progesteron receptors; pT – pathoanatomic primary tumor size.

Algorithm of adjuvant treatment in operable patients depending on presence or absence of regional metastases is showed in Table 3 and Table 4.

Table 3. Adjuvant treatment in patients without regional metastases.

Menstrual function	Low risk	High risk
Hormonosensitive tumors		
Premenopause	Tamoxifen or nothing	Cutoff ovarian function (or analog LH-RH) + tamoxifen (± chemotherapy), or chemotherapy + tamoxifen (±cutoff ovarian function (or analog LH-RH))
Postmenopause	Tamoxifen or nothing	Tamoxifen or chemotherapy+ tamoxifen
Hormonoresistant tumors		
Premenopause	–	Chemotherapy
Postmenopause	–	Chemotherapy

Table 4. Adjuvant treatment in patients with metastases in axillar lymph nodes.

Hormonosensitive tumors	
Premenopause	chemotherapy + tamoxifen (±cutoff ovarian function (or analog LH-RH)) or Cutoff ovarian function (or analog LH-RH) + tamoxifen (± chemotherapy)
Postmenopause	Chemotherapy+ tamoxifen

	Or Tamoxifen (aromatase inhibitors)
Hormonoresistant tumors	
Premenopause	Chemotherapy
Postmenopause	Chemotherapy

Reasonability of cutoff ovarian function with LH-RH for a two years period in patients with operable low risk BC in premenopause with N0 is under investigation.

In high risk BC patients, N0 and absence of hormone receptors 4-6 cycles of antracycline-based CT (AC, FAC) or 6 cycles CMF should be performed. Tamoxifen is prescribed for 5 years in premenopausal patients with positive receptors and after CT conduction. Alternative branch for this group could be cutoff ovarian function followed by tamoxifen.

In postmenopausal patients with N0 and positive hormone receptors tamoxifen is used for a 5 year period.

CT followed by tamoxifen is reasonable in high risk patients with in menopause. The basis of adjuvant treatment in patients older 70 years is tamoxifen.

In premenopause patients with N+ and less 4 involved lymph nodes 6 cycles of antracycline-based CT (CAF, FAC, AC) or 6 cycle of classic CMF with per oral cyclofosfamide should be performed. In case of 4 and more involved lymph nodes longer CT with taxans should be used. Later tamoxifen for 5 years should be prescribed in patients with hormonosensetive tumors.

Cutoff ovarian function with parallel tamoxifen taking is possible in patients with saved menstrual function, positive ER and PR, and less 4 involved lymph nodes.

The basis of adjuvant treatment in postmenopausal patients with positive hormone receptors is tamoxifen. In case of involvement of 4 and more lymph nodes CT followed by hormonotherapy is indicated. In negative receptor tumors only CT should be performed.

It’s proved that long time application of aromatase inhibitors (letrozole2.5 mg/day) in menopausal patients with receptor positive BC after the end of 5-year usage of tamoxifen improves hormonotherapy efficacy. It decreases the relative risk of relapse occurrence on 42 % by the results of 4-year observation.

Antracycline based CT in comparison with CMF decrease relapse risk on 12 %, death risk - on 11 % and improve 5-year RFS on 3.2 %, 5-year OS – on 2.7 %. Paclitaxel is using for adjuvant treatment after few cycles of antracycline based CT in patients with poor prognosis in the USA. European researches provide studies in docetaxel efficacy in adjuvant CT, which show its high effectiveness [28, 30].

The role of trastuzumab (Herzeptin) in adjuvant treatment of HER-2/neu+ BC patients was investigated in few randomized trials [28, 29, 31].

Thus, adjuvant hormonotherapy and CT improve OS and RFS in BC patients and permit return the patients to full-fledged work and social life thousands of Ukrainian woman.

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