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SYSTEMIC THERAPY OF EARLY BREAST CANCER

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Summary

Breast cancer is the most common cancer in women. Early breast cancer is potentially curable disease. Systemic adjuvant therapy is created to treat micrometastatic disease or destroy breast cancer cells that have spread from the breast and regional lymph nodes, but have not yet formed visible distant metastases. Systemic adjuvant therapy is based on chemotherapy with or without targeted therapy, and endocrine therapy, sometimes in combination with adjuvant irradiation, usually is conducted after surgery. The aim of adjuvant therapy is to decrease recurrence rate and extension of overall survival.

KEYWORDS: *breast cancer, micrometastasis, adjuvant chemotherapy, biological therapy, survival rate*

SUSTAVNO ANTINEOPLASTIČNO LIJEČENJE RAKA DOJKE

Sažetak

Rak dojke najčešća je zloćudna bolest u žena, potencijalno izlječiva u ranom stadiju. Sustavno adjuvantno liječenje osmišljeno je za uništenje mogućih mikrometastaza proširenih iz dojke i/ili iz regionalnih limfnih čvorova, koje još nisu stvorile vidljive udaljene metastaze. Temelji se na kemoterapiji sa ili bez ciljane biološke terapije, na endokrinoj terapiji, ponekad u kombinaciji sa zračenjem, obično nakon kirurškog zahvata. Cilj je smanjiti stopu povratka bolesti i produžiti život bolesnika.

KLJUČNE RIJEČI: *rak dojke, mikrometastaza, adjuvantna kemoterapija, biološko liječenje, stopa preživljenja*

Breast cancer is the major public health problem both in the world and in Croatia. It is the most common cancer in women and in 2011 the incidence in Croatia was about 94.4 new cases per 100 000, which is higher than in the European Union (68.8/100 000). Breast cancer is also the leading cause of death from malignancy in women with an annual rate of 40.3 cases per 100 000, while the mortality rate in the EU is almost twice as low (24.8/100 000) (1).

Introduction of mammography screening programs contributed to the increase in the number of newly diagnosed cases of breast cancer in the world and it led to the detection of breast cancer in an earlier stage. High mortality rate from breast cancer in Croatia is possibly consequence of a poor response to the national mammography program for early detection of breast cancer. The response has decreased by approximately 25% in the last few years. Around 70 000 preventive ex-

aminations of the breast were done in 2010, while in 2012 that figure decreased to about 50 000 (2).

Mortality from breast cancer in the developed world is decreasing which is not the case in Croatia (3). There are many factors which influence the prognosis of breast cancer, such as: axillary lymph node status, primary tumor size, presence of lymphovascular and perineuralinvasion, age, histological grade, tumor subtype, response to the primary neoadjuvant treatment, hormone receptor status and the presence of HER2 gene amplification. Number of involved axillary lymph nodes correlates with probability of cancer spread to the distant organs.

Patients with breast cancer which has not spread to the axilla have the overall 10-year survival rate of about 70%, while the 5-year disease recurrencerate in these patients is about 19%. In patients with positive axillary lymph nodes 5-year disease recurrence rate is 30% to 40% if they have 1 to 3 positive lymph nodes, 44% to 70% if they have 4 to 9 positive lymph nodes, and 72% to 82% if they have more than 10 positive nodes.

In order to reduce the probability of disease recurrence and death from breast cancer in patients in whom the disease was diagnosed in an early stage, adjuvant systemic antineoplastic treatment alone or in combination with adjuvant irradiation is applied after surgical procedure.

Adjuvant treatment of breast cancer is designed to treat micrometastatic disease or destroy breast cancer cells that have spread from the breast and regional lymph nodes, but have not yet formed visible distant metastases. Depending on the applied model of risk reduction, it is estimated that adjuvant treatment reduces mortality rates by 35% to 72%.

King and his colleagues proved a low rate of occult contralateral breast cancer cases and based on their study contralateral prophylactic mastectomy in average risk patients with newly diagnosed breast cancer is not recommended (4).

Standard adjuvant chemotherapy treatment includes a combination of cytotoxic drugs, i.e. polychemotherapy. Numerous clinical studies have shown that the use of adjuvant chemotherapy prolongs overall survival without disease recurrence, which is especially noted in hormone-independent disease, while the use of endocrine therapy prolongs overall and disease-free survival in patients with hormone-dependent tumors (5, 6).

The decision to use adjuvant treatment should be individualized and depend on the characteristics of patient and tumor, and should consider patients'comorbidities. It should be the result of teamwork. When making decision about systemic treatment, the most important prognostic factors are patient'sage, primary tumor size, grade, number of involved axillary lymph nodes and HER2 status (7). HER2 status is particularly important prognostic factor in patients with negative axillary lymph nodes (8). Today, there are methods which can, based on determining the genetic profile using the RT-PCR (Oncotype DX) or microarrays technology(MammaPrint), assess the risk of recurrence and predict the response to chemotherapy and endocrine therapy. Use of Oncotype DX and MammaPrint was evaluated in several studies and it was proved to be useful in predicting benefit from the addition of chemotherapy to endocrine therapy (9).

National Comprehensive Cancer Network (NCCN) guidelines for use of adjuvant systemic therapy are based on information about the size of the primary tumor, axillary lymph node status, hormone receptor status and HER2 gene amplification.Those guidelines does not recommend assessment of Ki67 as there is no conclusive evidence that Ki67 helps selecting the type of adjuvant therapy for individual patient.

On the contrary, European Society of Medical Oncology (ESMO) guidelines for breast cancer consider determining of Ki67 as one of the most important parameters.

For tumors smaller than 5 mm, which have notspread to axillary lymph nodes, the use of adjuvant therapy is of little importance. The use of endocrine therapy in patients with hormone-dependent tumors may be considered in terms of reducing the risk of developing contralateral breast cancer.

Patients with tumors size between 6 mm and 10 mm, which have not spread to the axillary lymph nodes, can be divided into low-risk and high-risk group. High-risk patients are those whose tumors show HER2 gene amplification, are hormone-independent, are high-grade and/or show lymphovascular or perineural invasion. In this group the decision on the type of therapy that will

be applied depends on the preference of the patient and balancing between the benefits and harms of therapy.

Patients with positive axillary lymph nodes or tumors larger than 10 mm are candidates for adjuvant systemic therapy. Patients with hormone-independent tumors larger than 10 mm and negative axillary lymph nodes are candidates for application of adjuvant chemotherapy. Patients with hormone-dependent tumors larger than 10 mm and negative axillary lymph nodes are candidates for adjuvant endocrine therapy and chemotherapy, however, in this group, the benefit of chemotherapy is relatively small (6).

Genetic profiling using Oncotype DX may be recommended to patients with hormone-dependent breast cancer larger than 10 mm, which shows no amplification of HER2, patients with grade 2 or 3 hormone-dependent tumors size between 6 mm and 10 mm, and patients whose tumor expresses other characteristics that indicate high risk (5,10,11).

According to the 2011 and 2013 St. Gallen guidelines the decision on the application of adjuvant chemotherapy depends, among other things, on the value of Ki67, which is one of the key elements in determining luminal subtype A and B in hormone-dependent tumors. According to European guidelines application of adjuvant chemotherapy is not indicated in almost all luminal A cases (ER positive, HER2 negative, Ki67<20%, PR>20%) except forhigh-risk tumors (tumor cells innumerous axillary lymph nodes). Effectiveness of chemotherapy is also unclear in the cases of luminal HER2 negative tumors (ER positive, HER2 negative and Ki67>20% or PR<20%) (11). Inthese groups of patients, genetic profiling may be performed to accurately assess potential benefits of application of adjuvant chemotherapy.

All patients with invasive, hormone-dependent breast cancer should receive adjuvant, postoperative, protective, endocrine therapy regardless of age, menopausal status, axillary lymph node status or the application of chemotherapy (13). Possible exception to this rule, could be a group of patients with hormone-dependent breast cancer smaller than 5 mm with negative axillary lymph nodes which shows good prognostic features because, in this group,long-term prognosis is so good that the benefit of adjuvant endocrine therapy is very small (6).

Based on retrospective analysis of paraffin tumor blocks collected in the ATAC study, it was proven that the presence of HER2 gene amplification indicates relative resistance to the use of endocrine therapy (14). However, in patients with HER2-positive and hormone-dependent tumors use of endocrine therapy is recommended.

The longest used and best researched endocrine therapy for premenopausal and postmenopausal women istamoxifen (9). Regardlessof application of adjuvant chemotherapy, prophylactic use of tamoxifen reduces the risk of recurrence and death from breast cancer. If patients are receiving chemotherapy and tamoxifen, chemotherapy is administered firstand is followed by tamoxifen (12). Numerous studies have shown that the use of tamoxifen for five years is more effective than the use for one to two years (14,15). Recently, the ATLAS study showed that prolonged use of tamoxifen for ten years compared to the standard use for five years reduces the risk of death from breast cancer, though we have to be aware of increased risk of endometrial cancer and pulmonary embolism (16). We are expecting the results of aTTom study whichalso compared standard five-year toten-yeartamoxifentherapy. Preliminary results indicate a non-significant reduction of local recurrence rate with ten-year treatment (17).

The role of ablation or suppression of ovarian function in adjuvant, postoperative, prophylactic treatment of breast cancer, whether we are referring to a surgical oophorectomy, irradiation or suppression using the LHRH agonists, has not yet been clearly defined (18-20). Although individual studies suggest clinical benefit from ablation or suppression of ovarian function in the adjuvant treatment of premenopausal patients with hormone-dependent breast cancer, the benefit of the addition of the aforementioned modalities of treatment to chemotherapy or tamoxifen is not clear or proven (19,21).

Several studies have compared the suppression of ovarian function with CMF chemotherapy protocol, and it was observed that in patients with hormone-dependent breast cancer antitumor activity of both modalities was equal, while in patients with hormone-independent breast cancer greater benefit was achieved by the use of chemo-

therapy. It was also observed thatthe younger premenopausal women had the greater benefit of suppressing ovarian function (21-29). None of these studies showed difference in the disease recurrence rate or survival rate (19,30,31).

Intergroup 0101 study compared the application of adjuvant chemotherapy with CAF protocol with CAF plus goserelin and CAF plus goserelin plus tamoxifen. It was observed that the addition of goserelin to chemotherapy extended the time to recurrence in comparison with chemotherapy only, but did not influence overall survival. This study, unfortunately, did not include a study group that received CAF plus tamoxifen, so the extent to which the use of goserelin prolongs the time to recurrence compared to standard endocrine therapy with tamoxifen,could not be assessed (22).

Several studies have investigated the application of aromatase inhibitors in the adjuvant treatment of postmenopausal patients with early breast cancer. Aromatase inhibitors in the adjuvant treatment may be administered as the initial therapy, as sequential therapy after two to three years of tamoxifen or as extended adjuvant therapy after 4.5 to 6 years of tamoxifen therapy.

There was no difference in survival between patients who received aromatase inhibitors as initial therapy compared to patients who received tamoxifen (32,33). ATAC study, however, showed that patients who initially received adjuvant endocrine therapy with anastrozole, had fewer cases of disease recurrence compared to patients initially receiving tamoxifen (32).

BIG 1-98 study investigated the initial and sequential treatment with an aromatase inhibitor compared to treatment with tamoxifen and showed that patients receiving letrozole had a prolonged time to relapse compared to those treated only with tamoxifen, but without affecting the overall survival (34).

Five studies investigated sequential use of third generation aromatase inhibitor after two to three years of treatment with tamoxifen. Studies that investigated the application of anastrozole (ITA, ABCSG trial 8, ARNO 95) after two to three years of adjuvant therapy with tamoxifen showed a prolongation of disease-free survival, and some of them the extension of overall survival, which was demonstrated by a meta-analysis of these three studies (35-38).

IES study showed that sequential use of exemestane after two to three years of tamoxifen prolongs disease-free survival and overall survival (39,40).

TEAM study compared the application of exemestane as initial therapy with sequential application of exemestane after two to three years of tamoxifen therapy, up to a total of 5 years of use (41). Results of this study are consistent with the results of the BIG 1-98 and they suggest that none of the described methods of application of adjuvant endocrine therapy is superior to another (34).

MA-17 study showed that prolonged therapy with letrozole after 4.5 to 6 years of tamoxifen reduces disease recurrence rate and occurrence of contralateral breast cancer, while in the group of patients with positive lymph nodes also prolongs overall survival (35,42).

Today we can not definitely say which model of adjuvant endocrine treatment is optimal - is it the initial application of aromatase inhibitor in postmenopausal patients, sequential use of tamoxifen and aromatase inhibitor or prolonged therapy with an aromatase inhibitor after about five years of adjuvant tamoxifen therapy. Also, it is still unclear what is the optimal duration of therapy with an aromatase inhibitor.

Recommendations for adjuvant treatment of postmenopausal patients at the time of diagnosisare: 1) an aromatase inhibitor as initial therapy for 5 years, 2) tamoxifen during two to three years followed by sequential administration of an aromatase inhibitor to a total of 5 years or use of an aromatase inhibitor for additional 5 years (least evidence of efficiency), 3) tamoxifen during 4.5 to 6 years followed by a prolonged treatment with an aromatase inhibitor over 5 years (if initially premenopausal patient becomes postmenopausal over the 5 years) or consider taking tamoxifen over total of 10 years (if the patient is initially premenopausal), taking into account the wishes of the patients.

Adjuvant chemotherapy is applied in order to prolong overall and disease-free survival. Adjuvant chemotherapy should be started within 2 to 6 weeks after the surgery because the literature data show a significant decrease in effectiveness when the application of adjuvant systemic therapy is postponed for more than 12 weeks after the surgery (43).

According to the National Comprehensive Cancer Network (NCCN) guidelines preferred adjuvant chemotherapeutic protocols for the treatment of breast cancer include: 1) dose-dense (common application) AC (doxorubicin, cyclophosphamide) with sequential use of dose-dense paclitaxel (every 2 weeks); 2) dose-dense AC with sequential use of weekly paclitaxel; 3) docetaxel and cyclophosphamide combination.

Two large randomized studies that have examined the addition of sequential paclitaxel to adjuvant chemotherapy with AC protocol in the patients with positive lymph nodes showed theprolongation of disease-free survival and overall survival. The advantage of paclitaxel was more expressed in patients with hormone-independent breast cancer (44,45). Besides preferred protocols, there are other protocols that may be applied in adjuvant treatment, depending on the characteristics of the patient, characteristics of the tumor and the patient wishes. All protocols listed and described below have been tested in randomized phase 3 clinical trials.

Large randomized study on almost 5000 patients who were classified into four groups (AC followed by a weekly paclitaxel/docetaxel or paclitaxel/docetaxel every 3 weeks) showed that; paclitaxel is most effective when used on a weekly basis - it prolongs overall survival compared to paclitaxel every 3 weeks; the use of docetaxel every 3 weeks is more effective compared to paclitaxel every 3 weeks or weekly docetaxel which prolongs disease-free survival,does not affect overall survival, but it is still less efficient compared to weekly paclitaxel (46).

Other study that examined adjuvant chemotherapy with dose-dense AC followed by paclitaxel every 2 weeks showed a prolongation of survival in comparison with AC protocol followed by paclitaxel every 3 weeks (47).

Based on these two studies the application of paclitaxel every 3 weeks after AC in the adjuvant treatment is not recommended in any guideline.

A study that compared adjuvant treatment with TC protocol (docetaxel, cyclophosphamide) with AC protocol has proved that the TC protocol significantly prolongs disease-free survival and overall survival compared to AC protocol (48).

It has been shown that there is no difference in disease-free survival and overall survival between use of adjuvant chemotherapy with AC protocol applied for four cycles and CMF (cyclophosphamide, methotrexate, 5-fluorouracil) protocol applied for six cycles (48-50).

Application of CMF chemotherapy significantly prolongs disease-free and overall survival in comparison with observation (5,51).

Studies that investigated adjuvant anthracycline-based chemotherapy have shown that it reduces the rate of disease recurrence and death from breast cancer and is recommended as the preferred therapy in patients with positive axillary lymph nodes. Those studies also emphasize the importance of applying the full dose of cytotoxic drugs (51,52).

Retrospective studies have shown that adjuvant anthracycline-based chemotherapy is more effective in patients with HER2-positive tumors compared to non-anthracycline-based chemotherapy (8).

One large study compared high dose CEF (cyclophosphamide, epirubicin 100 mg/m2, 5- fluorouracil) chemotherapy with CMF protocol in premenopausal patients with breast cancer and positive axillary lymph nodes. Results of this study showed a significant prolongation of survival without recurrence and overall survival in patients who received CEFas adjuvant therapy (53).

One study compared adjuvant FEC protocol for six cycles with three cycles of FEC followed by three cycles of docetaxel every 3 weeks in patients with positive lymph nodes and high-risk patients with negative lymph nodes. A group of patients who received docetaxel sequentially after FEC had significantly longer disease-free survival and overall survival (54).

It was also proven that the use of weekly paclitaxel after FEC is superior to the standard six cycles ofFEC in terms of reducing the risk of disease recurrence, but with no effect on overall survival (55).

When comparing adjuvant chemotherapy with TAC protocol (docetaxel, doxorubicin, cyclophosphamide)in patients with positive axillary lymph nodes with FACprotocol (5-fluorouracil, doxorubicin, cyclophosphamide), it has been proven that TAC significantly prolongs overall and disease-free survival. It is important to emphasize that the disease-free survival was the same in pa-

tients with hormone-dependent and hormone-independent tumors (56).

NSABP B-30 study compared TAC with AT (doxorubicin, docetaxel) and AC-T (doxorubicin, cyclophosphamide - docetaxel) adjuvant protocols. Results of this study showed that AC-T chemotherapy significantly prolongs disease-free survival but not overall survival compared to TAC protocol, and compared to AT protocol significantly prolongs both overall and disease-free survival (57).

The effect of the application of adjuvant chemotherapy is more significant in patients with hormone-independent breast cancer (5,10).

Therefore, the guidelines recommend consideration of the application of adjuvant chemotherapyfollowed by endocrine therapy in patients with hormone-dependent breast cancer with negative axillary lymph nodes, in patients with tumors larger than 10 mm which are HER2 negative and in patients with tumors between 6 mm and 10 mm, grade 2 or 3 or if tumor showsnegative prognostic features.

In patients whose tumors show HER2 protein overexpression, the addition of trastuzumab to adjuvant treatment significantly prolonged disease-free survival as well as overall survival (58). Trastuzumab is a humanized monoclonal antibody that specifically binds to the extracellular domain of the HER2 protein (59).

The NSABP B-31 study included patients with HER2-positive breast cancer who had positive axillary lymph nodes. Patients were randomized to receive AC during four cycles every 3 weeks followed by paclitaxel every 3 weeks for four cycles or to receive four cycles of AC followed by paclitaxel plus trastuzumab for four cycles, followed by trastuzumab alone for a total of one year.

The NCCTG N9831 trial enrolled patients with HER2-positive breast cancer who had positive axillary lymph nodes,patients who had negative axillary lymph nodes with primary hormone-independent tumor bigger than 10 mm and patients whose primary hormone-dependent tumor was larger than 20 mm. Patients were randomized similar to NSABP B-31 study except that paclitaxel was administered at weekly intervals for 12 weeks. In the subgroup of patients who received trastuzumab, it was administered together with paclitaxel and then once a week up to a total of 52 weeks.

Both of these studies showed a significant reduction of risk of disease recurrence and death from breast cancer by adding trastuzumabto adjuvant chemotherapy treatment (60). It is important to emphasize that in both studies patients who were treated with trastuzumab have had an increased rate of cardiotoxicity. However, cardiotoxicity was dependent on patients' age and initial cardiac systolic function. Increased rate of cardiotoxicity observed in adjuvant trials with trastuzumab was partly a consequence of pretentious cardiac function monitoring in these studies.

The third study that examined the effectiveness of trastuzumab in the adjuvant treatment was HERA study which compared the application of trastuzumab for one or two years. The patients included in this study had either positive or negative axillary lymph nodes with primary tumor larger than 10 mm (61). After a median follow-up of one year 46% reduction in the risk of recurrence was recorded. After a median follow-up of two years a significant difference in overall survival was recorded (62). After that moment, the patients who were primarily randomized to receive chemotherapy alone were allowed to cross over and to receive trastuzumab subsequently. After a median follow-up of eight years there was no significant difference in disease-free survival between patients who received trastuzumab for one and two years (63). Therefore, the standard time of application of adjuvant trastuzumab is one year.

The BCIRG 006 trial enrolled women with HER2-positive breast cancer with positive axillary lymph nodes or high-risk women with negative lymph nodes. Patients were randomized to receive either the AC followed by docetaxel (AC-T) or AC followed by docetaxel with trastuzumab (AC-TH) and then trastuzumab monotherapy during one year or were randomized to receive docetaxel, carboplatin and trastuzumab (TCH) up to a total of one year of trastuzumab (58). In both trastuzumab groups overall survival was longer than in the control group. Cardiotoxicity rate was significantly lower in the TCH group compared to the AC-TH group. In the TCH group slightly higher number of distant disease recurrences was found compared to the AC-TH group.

The FinHer study included patients with HER2-positive breast tumors and positive axillary lymph nodes and patients with negative axillary lymph nodes with tumors larger than 2 cm and negative progesterone receptors. Patients were randomized to receive nine weekly vinorelbine or three docetaxel every three weeks, which was followed by three cycles of FEC. One part of patients in both groups was randomized to receive trastuzumab over nine weeks with assigned chemotherapy protocol – docetaxel or vinorelbine. Results of the study showed that the addition of trastuzumab reduces the risk of recurrence, but does not affect overall survival. FinHer is the only study of adjuvant trastuzumab, which was sponsored by Finland government and not by large pharmaceutical companies, which showed that short adjuvant trastuzumab treatment does not significantly affect survival.

Described adjuvant trastuzumab studies have shown that its addition to adjuvant treatment significantly prolongsdisease-free survival. Meta-analysis of three of these studies (NSABP B-31, NCCTG N9831, HERA) revealed that addition of trastuzumab also prolongs overall survival in high-risk patients with HER2-positive breast cancer. The usefulness of trastuzumab is independent of the tumor hormone receptor status (64,65,66).

In FNCLCC-PACS-04 study five hundred HER2 positive women with positive axillary lymph nodes were randomized to receive trastuzumab sequentially after adjuvant chemotherapy based on anthracycline with or without docetaxelor just to be observed. Results of the study showed no significant prolongation of overall or disease-free survival with sequential addition of trastuzumab (67). Sequential application of trastuzumab after chemotherapy is not effective as the concomitant chemotherapy with trastuzumab.

NCCN strongly recommends the application of trastuzumab together with chemotherapy in the adjuvant treatment of breast cancer patients with HER2-positive tumors larger than 1 cm and in patients with HER2-positive tumors size between 6 mm and 10 mm, which are associated with micrometastasis in the axillary lymph nodes (tumor deposit in the axilla smaller than 2mm). For smaller tumors application of trastuzumab with chemotherapy is a matter of individual assessment.

Protocols that are recommended in the adjuvant treatment of HER2 positive disease are AC protocol followed by paclitaxel with trastuzumab over 12 weeks and TCH protocol in patients at risk for developingcardiotoxicity. Also trastuzumab can be combined with weekly paclitaxel over 12 weeks in patients with small tumors and negative axillary lymph nodes. Trastuzumab should be continued up to one year starting from the first dose of taxane chemotherapy.

In addition to the above listed preferred protocols, AC protocol followed by docetaxel with trastuzumab to a total of one year of trastuzumab may be also applied in patients with HER2-positive tumors (58). The use of adjuvant anthracycline-based chemotherapy followed by sequential trastuzumabis not recommended (67). Considering the cumulative cardiotoxicity simultaneous, concomitant use of trastuzumab and anthracyclinesis not recommended except within clinical studies.

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