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SYSTEMIC THERAPY OF METASTATIC BREAST CANCER

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Summary

Systemic therapy of metastatic breast cancer is not curative and its goal is life prolongation and improvement of quality of life. Treatment of metastatic breast cancer usually involvesendocrine therapy and/or chemotherapy with or without targeted therapy. The use of the minimally toxic endocrine therapies is preffered to the use of cytotoxic therapy whenever reasonable.

KEY WORDS: *breast cancer, hormone therapy, cytotoxic agents, biological therapy, bisphosphonates*

SUSTAVNO ANTINEOPLASTIČNO LIJEČENJE METASTATSKOG RAKA DOJKE

Sažetak

Sustavno liječenje metastatskog raka dojke nije kurativno već se provodi u svrhu produženja života i poboljšanja kvalitete života. Sustavno liječenje se sastoji od endokrine terapije i/ili kemoterapije uz ili bez primjene ciljane biološke terapije. U liječenju metastatskog raka dojke preferirani oblici liječenja su oni najmanje toksični te se endokrina terapija primjenjuje kad god je to moguće.

KLJUČNE RIJEČI: *karcinom dojke, hormonska terapija, citotoksični lijekovi, biološka terapija, bisfosfonati*

Metastatic breast cancer is an incurable disease so the goal of treatment is to prolong patients' life and improve its quality. Depending on a number of factors, such as immunohistological type of disease, location of metastases, patients' condition and previous treatment, different types of therapy listed hereafter could be used.

I. Endocrine therapy

Endocrine therapy should generally be considered as initial treatment for a breast cancer patient with metastatic disease: if the patient's tumor is estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, or ER/PR-unknown; if the patients disease involves only bones and soft tissue and if the patient either received no adjuvant antiestrogen therapy or if such therapy has not been applied for more than 1 year (1). Patients with lymphangitic pulmonary metastases, major liver involvement and/or central nervous system involvement should not receive endocrine therapy as a single treatment modality. Early failure

(e.g.<6 months) ofendocrine therapy suggests that cytotoxic chemotherapy should be used as the next modality of treatment. Some premenopausal women should undergo oophorectomy (surgically, with external-beam radiation therapy or with a LHRH agonist) (2).Endocrine therapy may be also active in patients with negative ER and PR receptors, especially on primary tumor and in softtissue disease and/or bone-dominant disease (3-5).

In premenopausal women, endocrine therapies include selective estrogen receptor modulators (SERMs) (tamoxifen or toremifene), luteinizing hormone-releasing hormone (LHRH) agonists (goserelin and leuprolide), surgical or radiotherapeutic oophorectomy, progestin (megestrol acetate), androgens (fluoxymesterone), and high-dose estrogen (ethinylestradiol). For most premenopausal patients, following therapy with tamoxifen, the use of ovarian suppression or ablation in combination with endocrine therapy for postmenopausal women is appropriate.

First-line endocrine therapy in postmenopausal women includesaromatase inhibitors (AI): nonsteroidalaromatase inhibitors (anastrozole, letrozole) andsteroidal aromatase inhibitors (exemestane), selective ER modulators (tamoxifen, toremifene), ER down regulators (fulvestrant), progestin (megestrol acetate), androgens (fluoxymesterone), and high-dose estrogens (ethinylestradiol) and some new recently approved combinations. While tamoxifen has been used in this setting for many years, several randomized trials suggest equivalent or superior response rate (RR) and progression free survival (PFS) for the AIs compared to tamoxifenas well as better tolerability (less thromboembolic events and vaginal bleeding). In comparison to megestrol acetate, all three currently available aromatase inhibitors have demonstrated, in prospective randomized trials, at least equal efficacy and better tolerability (10-20). In a meta-analysis that included randomized trials in patients who were receiving an AI as either their first or second line ofendocrine therapy for metastatic disease, those who were randomly assigned to a selective AI lived longer (HR for death, 0.87; 95% CI, 0.82–0.93) than those who received standard therapy (tamoxifen or a progestational agent) (21). Several randomized but underpowered trials have tried to determine if combined endocrine therapy (LHRH agonists plustamoxifen) is superior to any monotherapy in premenopausal women. Results have been inconsistent (22-25). Two randomized trials that enrolled patients who had progressed after receiving tamoxifen demonstrated that fulvestrant yielded similar results to anastrozole in terms of its impact on PFS (26,27). The updated follow-up results showed an improved time to progression (TTP) with fulvestrant 500 mg compared to anastrozole (median TTP 23.4 months for fulvestrant vs. 13.1 months for anastrozole; HR, 0.63; 95% CI, 0.39–1.00; P=0.0496). Fulvestrant appears to be at least as effective as anastrozole in patients whose disease progressed on previous tamoxifen, and a reanalysis of these studies suggested a longer duration of response favoring fulvestrant (28). The proper sequencing of these therapies is currently not known (29). Phase III randomized study (CONFIRM) compared fulvestrant 500 mg monthly versus fulvestrant 250 mg monthly. The PFS was superior with the fulvestrant 500 mg regimen (HR 0.80; 95% CI, 0.68–0.94; P= .006) and the final analyses demonstrated an increase in median OS (4.1 months) and reduced risk of death (19%) with a dose of 500 mg compared to 250 mg. Median OS was 26.4 vs. 22.3 months (HR: 0.81; 95% CI: 0.69-0.96; P= .016) (30). Two studies documented a PFS advantage when adding trastuzumabto anastrozole (TANDEM study) or lapatinib to letrozole in postmenopausal women with HR-positive, HER2-positive metastatic breast cancer. Overall survival showed no statistically significant difference and adverse effects (AEs) were more frequent with the combination (31,32).

However, patients inevitably develop resistance to endocrine therapy. The clinical benefit rates of exemestane and fulvestrant observed in a phase III trial of postmenopausal women with HR-positive advanced breast cancer who experienced disease progression on prior non-steroidal AI therapy were comparable (32.2% vs. 31.5%; P = 0.853) (33).While there is a biologic rationale for combining fulvestrant with a third-generation aromatase inhibitor for patients with non-steroidal AI resistant disease, the benefits of such combination therapy have not been established (SoFEA trial) (34). One mechanism of resistance to endocrine therapy is activation of the mammalian target of rapamycin (mTOR) signal transduction pathway. BOLERO-2is a randomized, phase III

trial, of randomly assigned patients with HR-positive metastatic breast cancer resistant to non-steroidal AI who received the mTOR inhibitor everolimus plus exemestane versus placebo plus exemestane. Median PFS was 6.9 months for everolimus plus exemestane and 2.8 months for placebo plus exemestane (HR, 0.43; 95% CI, 0.35–0.54; *P*< .001). Final OS outcomes are awaited. The addition of everolimus was found to be more toxic with common grade 3 or 4 AE which included stomatitis, anemia, dyspnea, hyperglycemia, fatigue, and pneumonitis (35).

After second-line endocrine therapy, little high-level evidence exists to assist in selecting the optimal sequence of endocrine therapy.

II. Cytotoxic chemotherapy

Candidates for cytotoxic chemotherapy are patients with hormone receptor–negative tumors, those with visceral metastases andpatients whose tumors have progressed on endocrine therapy (36). Single agents that have shown activity in metastatic breast cancer are:

Anthracyclines: doxorubicin, epirubicin, liposomal doxorubicin (37-40), mitomycin.

Microtubuleinhibitors: taxanes [paclitaxel (41,42), nanoparticle albumin-boundpaclitaxel (43,44), docetaxel], vinca alkaloids [vinorelbine (45), vinblastine], eribulin (46,47).

Alkylating agents: cyclophosphamide, carboplatin, cisplatin.

Antimetabolites: fluoropyrimidines [5-FU and capecitabine (48-50)], gemcitabine (51).

Combination regimens that have shown activity in metastatic breast cancer are:

Cyclophosphamide/doxorubicin (52), epirubicin/doxorubicin (53), cyclophosphamide/doxorubicin/5-fluorouracil (54), cyclophosphamide/epirubicin/5-fluorouracil (55), cyclophosphamide/methotrexate/5-fluorouracil (56), docetaxel/doxorubicin (57), paclitaxel/doxorubicin (58,59), docetaxel/capecitabine (60), vinorelbine/epirubicin (61), capecitabine/ixabepilone (62), gemcitabine/paclitaksel (63), gemcitabine/carboplatin (64).

It is unclear which of single-agent chemotherapy or combination chemotherapy is preferable for first-line treatment. An Eastern Cooperative Oncology Intergroup study randomly assigned patients to receive paclitaxel and doxorubicin given both as a combination and sequentially (65). Although RR and TTP were both better for the combination, OS was the same in both groups (66-68). Considering that there is no data on supporting the superiority of any particular regimen.The rate of disease progression, comorbid medical conditions, and physician/patient preference will influence the choice of therapy in individual patients.

Combinations of chemotherapy and endocrine therapy have not shown an OS advantage over the sequential use of these agents (1,69). The addition of one or more chemotherapy drugs to a chemotherapy regimen in the attempt to intensify the treatment improved RR but had no effect on OS (70). The optimal treatment duration for patients with responsive disease has been studied by several groups.Studies indicate that additional chemotherapy, immediately following patients best response to an induction chemotherapy regimen, does not improve OS (71-73).

Studies comparing high-dose (HD) chemotherapy with stem cell support to conventional chemotherapy in patients with metastatic disease indicate no OS orrelaps free survival (RFS) benefit for patients receiving HD chemotherapy (74-77). The potential doxorubicin-induced cardiac toxic effects should be considered in the selection of chemotherapeutic regimens for an individual patient. Recognized risk factors for cardiac toxicity include advanced age, prior chest-wall radiation therapy, prior anthracycline exposure, hypertension, diabetes, and known underlying heart disease.

The cardioprotective drug, dexrazoxane, has been shown to decrease the risk of doxorubicin-induced cardiac toxicity, it permitted patients to receive greater cumulative doses of doxorubicin and allowed patients with cardiac risk factors to receive doxorubicin. Dexrazoxane has a similar protective effect in patients receiving epirubicin. The risks of cardiac toxicity may be reduced by administering doxorubicin as a continuous intravenous infusion (78-83).

III. Targeted therapy

Targeted therapies are drugs that block the growth and spread of cancer by interfering with

specific molecules involved in tumor growth and progression. There are two main types of targeted therapy drugs which can be used in breast cancer:

Monoclonal antibodies: trastuzumab, bevacizumab, pertuzumab.

Small molecules (tyrosine-kinase inhibitors): lapatinib.

Trastuzumab - approximately 20% of patients with breast cancer have tumors that overexpress HER2/neu protein. Trastuzumab is a humanized monoclonal antibody that binds to the HER2 receptor (84). In patients previously treated with cytotoxic chemotherapy whose tumors overexpress HER2/neu protein, administration of trastuzumab as a single agent resulted in a response rate of 21% (85). In a prospective trial, patients with metastatic disease were randomly assigned to receive either chemotherapy alone (doxorubicin and cyclophosphamide or paclitaxel) or the same chemotherapy and trastuzumab. Patients treated with chemotherapy plus trastuzumab had an OS advantage compared to those receiving chemotherapy alone (25.1 months vs. 20.3 months, P=0.05) (86). When combined with doxorubicin, trastuzumab is associated with significant cardiac toxicity (87). Consequently, patients with metastatic breast cancer with substantial overexpression of HER2/neuprotein are candidates for treatment with the combination of trastuzumab and paclitaxel or for clinical studies includingtrastuzumab combined with taxanes and other chemotherapeutic agents (88). Clinical trials that comparedmultiagent chemotherapy plus trastuzumabto single-agent chemotherapy have yielded conflicting results (89,90). Outside of a clinical trial, standard first-line treatment for metastatic HER2-overexpressing breast cancer should consist of single-agent chemotherapy plus trastuzumab.

Ado-TrastuzumabEmtansine(T-DM1) - is an antibody-drug conjugate that incorporates the HER2–targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1. T-DM1 allows specific intracellular drug delivery to HER2-overexpressing cells, potentially improving the therapeutic index and minimizing exposure of normal tissue. The phase III randomized study (EMILIA) enrolled 991 patients with HER2-overexpressing, unresectable, locally advanced or metastatic breast cancer who were previously treated with trastuzumab and a taxane (91).Patients were randomly assigned to T-DM1 orlapatinib plus capecitabine. Median PFS was 9.6 months with T-DM1 versus 6.4 months with lapatinib plus capecitabine (HR, 0.65; 95% CI, 0.55–0.77; P<0.001). Median OS crossed the stopping boundary for efficacy (30.9 months vs. 25.1 months; HR, 0.68; 95% CI, 0.55–0.85; P<0.001). The incidences of thrombocytopenia and increased serum aminotransferase levels were higher in patients who received T-DM1, whereas the incidences of diarrhea, nausea, vomiting, and palmar–plantar syndrome were higher in patients who received lapatinib plus capecitabine.

Pertuzumab - is a humanized, monoclonal antibody that binds to a different epitope of the HER2 extracellular domain than trastuzumab does. The binding of pertuzumab to HER2 prevents dimerization with other ligand-activated HER receptors, most notably HER3. The phase III CLEOPATRAtrial assessed the efficacy and safety of pertuzumab plus trastuzumab plus docetaxel versus placebo plus trastuzumab plus docetaxel, in the first-line HER2+ metastatic setting (92). The median PFS was 12.4 months in the control group versus 18.5 months in the pertuzumab group (HR, 0.62; 95% CI, 0.51–0.75; P<0.001). At the median follow-up of 30 months the results showed statistically significant improvement in OS in favour of pertuzumab containing regimen, with 34% reduction in the risk of death. At median follow-up of 50 months (range 0 to 70 months), the statistically significant improvement in OS in favour of pertuzumab/trastuzumab/docetaxel arm was maintained (HR = 0.68, P= 0.0002). Median OS was 40.8 months in the placebo arm and 56.5 months in the pertuzumab arm, with difference of 15.7 months. The toxicity profile was similar in both treatment groups with no increase in cardiac toxic effects seen in the pertuzumab combination arm.

Bevacizumab – is a humanized monoclonal antibody directed against all isoforms of vascular endothelial growth factor-A. Its role in the treatment of metastatic breast cancer remains controversial. The efficacy and safety of bevacizumab as a second- and third-line treatment for patients with metastatic breast cancer were studied in several randomized, phase III trials (e.g. ECOG-2100, AVADO, RIBBON 1, RIBBON 2) (93-97). Based on the consistent finding that bevacizumab only

modestly improved PFS but not OS, and given its considerable toxicity profile (e.g. hypertension, proteinuria), the Food and Drug Administration (FDA) revoked approvalof bevacizumab for the treatment of metastatic breast cancer.

Lapatinib - is an orally administered tyrosine kinase inhibitor of both HER2/neu and the epidermal growth factor receptor.Lapatinib has shown activity in combination with capecitabine in patients who have HER2-positive metastatic breast cancer refractory to trastuzumab.A non-blinded, randomized trial compared the combination of capecitabine and lapatinib with capecitabine alone in 324 patients with locally advanced or metastatic disease that progressed to therapies that included anthracyclines, taxanes, and trastuzumab. Highly significant difference was found that favored the combination arm with respect to the primary study endpoint and time to progression (median time to progression 8.4 months vs. 4.4 months; HR, 0.49; 95% CI, 0.34–0.71; P<0.001). There was no difference in OS (HR, 0.92; 95% CI, 0.58–1.46; P= 0.72) (98). Patients randomized to combination therapy were more likely to develop diarrhea, rash, and dyspepsia.

The combination of lapatinib and trastuzumab has been evaluated for patients with HER2-positive metastatic breast cancer whose disease progressed while they were being treated with trastuzumab in a phase III trial (99). A total of 291 patients were randomly assigned to treatment with lapatinib alone or to combination with trastuzumab. Compared with lapatinib alone, the combination of lapatinib and trastuzumab significantly improved PFS (HR, 0.74; 95% CI, 0.58–0.94; median, 11 weeks vs. 8 weeks) and OS (HR, 0.74; 95% CI, 0.57–0.97; median, 14 months vs. 10 months). The control arm, lapatinib alone is a nonstandard treatment arm.

These data offer heavily pretreated metastatic HER2-positive breast cancer patients an alternative chemotherapy-free treatment regimen using dual HER2 blockade. Randomized phase III study compared paclitaxel and lapatinib with paclitaxel plus placebo as first-line therapy in patients with metastatic breast cancer, but no benefit was found with the combination treatment. Toxicities, specifically alopecia, diarrhea, and rash were higher in the HER2/neu-positive lapatinib group (100).

IV. Supportive therapy for bone metastases

The **bisphosphonates** and **denosumab** may be used as supportive therapy to reduce skeletal related events (SREs) in patients with bone metastases (101). Results of randomized trials of pamidronate and clodronate in patients with bone metastaseshave shown decreased skeletal morbidity (102-104). Zoledronate has been at least as effective as pamidronate (105). Denosumab has better activity compared to zolendronate. This is based upon the results of a single randomized trial where denosumab was shown to significantly delay time to first SRE (HR, 0.82; 95% CI, 0.71–0.95; *P*<.001). No difference in TTP or OS was observed (106). Both, the bisphosphonates and denosumab, are associated with the occurrence of osteonecrosis of the jaw (ONJ). Poor baseline dental health or dental procedures during treatment are known risk factors for ONJ (107).

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