ORIGINAL ARTICLE

Effects of adding taxane to anthracycline-based neoadjuvant chemotherapy in locally advanced breast cancer

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ABSTRACT

Aim To compare the effect of neoadjuvant chemotherapy based on taxane and/or anthracycline to the extent of an objective response in female patients with unresectable breast cancer with evaluation of the toxic profile of applied chemotherapy.

Methods One hundred patients with histologically verified breast cancer, treated with neoadjuvant chemotherapy were divided into two groups: a study group A (50 patients), who had received 4 to 6 cycles of taxane-based chemotherapy, and control group B (50 patients), who had received 4 to 6 cycles of anthracyclines-based chemotherapy. Pathohistological response was evaluated after tumour excision and axillary resection at the end of chemotherapy and it was defined as pathologic complete (pCR), partial (pPR), or no response (pNR). Toxic effects were evaluated and quantified by the Common Terminology Criteria for Adverse Events v4.0.

Results After neoadjuvant chemotherapy, 8% of patients in the group A achieved pCR, 54% achieved pPR, while 38% of patients had no tumour response to applied chemotherapy. In the group B pCR was achieved in 6%, pPR in 42% of patients, while 51% of patients were pNR to the administered chemotherapy. Significant reduction of tumour mass was achieved in the group of patients treated with taxanes: 20.00 (7.75-30.25) vs. 13.50 (6.00-25.00) mm (p=0.024). Toxicity of chemotherapy in group A and group B was within the limits of grade 2.

Conclusion The addition of taxane to anthracycline-based neoadjuvant chemotherapy in patients with breast cancer resulted in a significant reduction in tumour mass compared to the group of patients treated with anthracyclines, but without increasing the overall side effects.

Key words: tumour reduction, anthracyclines, taxanes

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INTRODUCTION

Breast cancer is the most common malignant tumour in women and the second leading cause of cancer death in women (1,2). The mortality rate is about 20.5% with tendency of decrease in the last two decades (3).

Radical mastectomy has long been the leading method in treating breast cancer. Neoadjuvant (preoperative, primary or induction) chemotherapy (NACT) was introduced in early 1970s to treat unresectable, advanced breast cancer. Application of NACT is becoming increasingly common in ≥3cm in size and locally advanced (T3, T4 or N2) breast cancer for the purpose of so called "down staging" approach aiming to achieve the reduction in tumour size for better operative outcome and better survival rate (4,5).

The use of anthracyclines (from *Streptomyces peucetius*) in 1980s showed targeted effects on topoisomerase II (Top2), biding it to the DNA with high affinity leading to stabilization of DNA-Top2 complex and double-strand DNA break (6). The anthracycline kinone structure supports the catalysis of oxidation and reduction reactions and the formation of oxygen free radicals that are likely to be involved in antitumor effects as well as the toxicity associated with these drugs (7).

An interest in taxanes began in 1963 when the extract from *Taxus brevifolia* plant showed impressive activity in pre-clinical tumour models. Taxanes vary the degree of tubulin separation constantly on both microtubule ends, thus increasing the dynamic instability (4). The ability of taxanes to induce mitotic interruption is associated with microtubule binding, which is already apparent in submicromolar concentrations (4).

Based on a broad spectrum of clinical studies over the last decade, neoadjuvant chemotherapy (NACT) has shown to increase the breast-conserving surgery and to reduce the mortality rate, however, with the small number of pathological complete responses. Due to promising outcomes, taxanes were incorporated in adjuvant treatment in early breast cancer combined with or sequentially after anthracycline therapy (8,9). In our oncology practice we have applied anthracycline and taxane based neoadjuvant chemotherapy since 2007 in a heterogeneous patient population with advanced breast cancer, which imposed the need for a systematic evaluation of the effects of this type of chemotherapy on the size of pathohistological response and the safety of its use in locally advanced breast cancer.

The aim of this study was to compare the effect of anthracycline and/or taxane based neoadjuvant chemotherapy on the extent of objective responses in female patients with unresectable breast cancer as well as to evaluate and compare the toxic profiles of both chemotherapy regimens.

PATIENTS AND METHODS

Patients and study design

Female patients treated with neoadjuvant chemotherapy based on anthracycline or taxane due to patohistologically confirmed breast cancer were included in a retrospective-prospective manipulative observational study in the period from January 2010 until June 2014 at the Clinic for Oncology at the Clinical Centre of Sarajevo University. Patients were selected based on similar clinical features (clinical stage of the disease, histological type, tumour molecular profiling, age). Data on tumour features (TNM and molecular profile), type of neoadjuvant chemotherapy and the size of overall tumour response that was evaluated by radiological examination of tumour size (RECIST classification) (10) prior to initiation of chemotherapy and after 4 to 6 cycles of therapy were obtained from the history of patients. According to the type of neoadjuvant therapy, the patients were divided into two groups: study group (A) - 50 patients who received 4 to 6 cycles of taxane-based neoadjuvant chemotherapy and a control group (B) - 50 patients who received 4 to 6 cycles of anthracycline-based neoadjuvant chemotherapy.

Methods

Patohistological verification of cancer was done after the core biopsy of initial tumour change. Determining the stage of breast cancer was done based on clinical and radiological findings (mammography, ultrasound, RTG or lung CT scan, CT or MRI of abdomen), and patohistological staging (11): class 1- disappearance of all tumour either on macroscopic or microscopic assessment; class 2 - presence of in situ carcinoma; class 3 - presence of invasive carcinoma with stromal alteration such as sclerosis or fibrosis; class 4 - no or few modifications of the tumoral appearance.

Laboratory findings (hematological, biochemical, coagulation factors) and heart ultrasound with determination of ejection fraction of left ventricle (EFLV) were performed on all patients prior to initiation of chemotherapy. After each chemotherapy cycle and before the next cycle, side effects have been recorded and laboratory findings were verified.

The extent of tumour response was clinically monitored after each cycle, and radiologically after three cycles, using the same method as was used initially (mammography, ultrasound or MRI) until completing the chemotherapy protocol. Patohistological response was evaluated after tumour excision or mastectomy and axillary lymph node dissection. Pathologic response rate to neoadjuvant chemotherapy was assessed as complete (CR), partial (pPR) or no response (pNR) as per Response Evaluation Criteria in Solid Tumours v4.0, RECIST classification (10). Pathologic complete responses (pCR) was defined as having no residual invasive carcinoma in the breast and no tumour in axillary lymph nodes at the end of chemotherapy or pathological lymph nodes (whether targeted or nor-targeted) with reduction in short axis <10 mm. Isolated tumour cells (ITC) were allowed in the determination of pCR. Any pathologic partial response (pPR) was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters, while no response (pNR) have included patients without a pathological therapeutic response or at least a 20% increase in the sum of diameters of target lesions. Toxic effects were evaluated and quantified by the Common Terminology Criteria for Adverse Events (AE) v4.0 (CTCAE), e.g. descriptive terminology of grading (severity) scale for each AE term: nausea grade 1- loss of appetite without alteration in eating habits; nausea grade 2 - oral intake decreased without significant weight loss, dehydration or malnutrition; vomiting grade 1 - intervention not indicated; vomiting grade 2 - outpatient IV hydration; medical intervention indicated (12).

Statistical analysis

Statistical analysis of the obtained data was performed using the Minitab 17 Software for Windows (Minitab, Inc. 2014). The normality of data distribution was determined by Shapiro-Wilk test. All data were expressed as median and interquartile range. Mann Whitney U test was used to compare the differences in parameters between the two observed groups, while Wilcoxon test was applied in testing the difference between the initial and residual tumour mass within the treated groups. The results are shown as median values with an interquartile range (IQR). $\chi 2$ test was used to examine differences between groups in the observed properties. The level of significance was set at $p<0.05$.

RESULTS

Among 100 female patients the most common type of breast cancer was ductal invasive carcinoma, in 78 (78%) patients. Stage analysis of breast cancer in both chemotherapy groups showed the highest incidence of stage IIIA, 67 (67%, with the ratio 62:72% between group A and group B). Out of 100 patients, 14 (14%) had stage IIB breast cancer, while seven (7%) had stage IIIB. The majority of patients in both groups, 61 (61%) had grade 2 breast cancer; no statistically significant difference was found as to the frequency of different tumour grades in both chemotherapy groups ($p= 0.656$).

Significant reduction of initial tumour mass in the group of patients treated with anthracycline, 40.00 (30.00-55.25) vs. 26.50 (19.25-38.50) mm ($p<0.001$) as well as in the group of patients treated with taxane, 40.00 (30.00-60.00) vs. 25.00 (17.50-45.00) mm ($p<0.001$) was found (Figure 1). But, realized difference in tumour mass was significantly higher in the group of breast cancer patients treated with taxanes compared to the group of breast cancer patients treated with anthracycline, 20.00 (7.75-30.25) vs. 13.50 (6.00-25.00) mm ($p=0.024$) (Figure 2).

Based on the achieved response to chemotherapy regimen, the patients were classified as follows: no pathological response (pNR), partial respon-

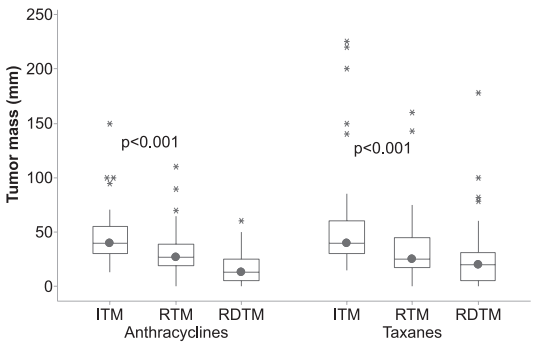

Figure 1. The difference in tumour mass within the breast cancer patient groups treated with anthracyclines or taxanes chemotherapy regimen; ITM, initial tumour mass; RTM, residual tumour mass; RDTM, realized difference in tumour mass

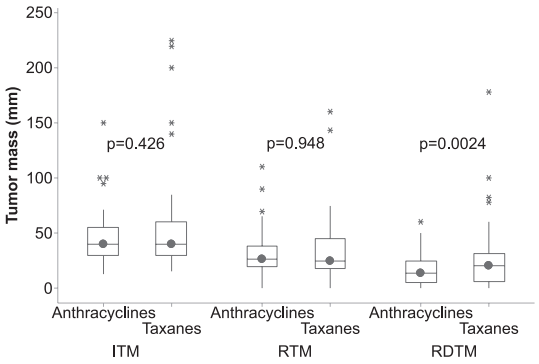

Figure 2. The difference in tumour mass in relation to the type of chemotherapy; ITM, initial tumour mass; RTM, residual tumour mass; RDTM, realized difference in tumour mass

se (pPR) and complete response (pCR). The statistical analysis did not show any significant difference in the frequency of specific forms of therapy responses between the two tested groups (p= 0.371). After neoadjuvant chemotherapy, four (8%) patients in the study group (A) /taxane/ achieved complete pathological response, 27 (54%) achieved partial response, and 19 (38%) of patients had no tumour response to the administered chemotherapy. A total of three (6%) patients in the control group (B) /anthracycline/ achieved complete pathological response, 21 (42%) achieved partial pathological response, and 26 (51%) patients had no tumour response to the administered chemotherapy.

The chemotherapy toxicity in both groups (study and control) was within the limits of grade 2. Adding taxanes to anthracyclines did not increase the overall side effects (Table 1).

Table 1. Adverse effects of chemotherapy according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.0

Gradus (G) of adverse effect	No (%) of patients with therapy		p
	Anthracyclines	Anthracyclines plus taxanes	
nausea G1	10 (20)	12 (24)	0.629
nausea G2	17 (34)	13 (26)	0.383
vomiting G1	8 (16)	10 (20)	0.650
vomiting G2	27 (54)	23 (46)	0.639
diarrhoea G1	11 (22)	12 (24)	0.709
hair loss	50 (100)	45 (90)	0.090
mucositis G2	7 (14)	8 (16)	0.758
change of taste of food G1	17 (34)	19 (38)	0.950
stomatitis G1	3 (6)	3 (6)	1.000
loss of appetite G1	1 (34)	19 (38)	0.963
bone ache	11 (22)	22 (44)	0.019
weakness G2	7 (14)	9 (18)	0.991
peripheral neurotoxicity G1/2	1 (2)	27 (54)	0.001
neutropenia G1	7 (14)	3 (6)	0.552

In 13 (26%) patients in the taxane-based study group grade 2 nausea was induced, and in 12 (24%) of patients grade 1 nausea was present. The frequency of grade 1 vomiting was present in 10 (20%) patients in the control group, and grade 2 vomiting in 23 (34%) patients (p>0.05). There were no side effects such as grade 3 and 4 vomiting. A higher level of cytopenia was observed in the anthracycline group, seven (14%). Peripheral neurotoxicity was statistically significantly higher in taxane group with grade ½, in 27(54%) patients (p<0.001) as well as occurrence of bone ache (p=0.019).

DISCUSSION

The possibility to administer neoadjuvant therapy provides direct information on the clinical (*in vivo*) and pathological response to the therapy. Introduction of postoperative radiotherapy increased the local control of the disease and survival rate, while the combination of systematic chemotherapy with surgery and/or radiotherapy provided even better results, making this approach a standard treatment for patients with locally advanced breast cancer but without satisfactory long-term outcomes (35-55% of local recurrences and 25-45% of five-year survival) (13). A large number of clinical studies have shown that the size of the pathologically detected residual disease and any evidence of residual cancer *in situ* or invasive in the breast and surrounding lymph nodes (after neoadjuvant chemotherapy) is associated with the result of long-term prognosis (8, 14-16). However, no agreement was reached on the precise definition of pathological complete response (pCR).

Changing trends in the treatment of locally advanced breast cancer directly depends on new findings in understanding the biology of the disease (13). In our study, the most common histological type of breast cancer was ductal invasive cancer, and the most common stage of breast cancer was IIIA stage. After neoadjuvant chemotherapy, a complete and partial pathological response was achieved more in the study (A) group (taxane) compared to control (B) group (anthracyclines). With respect to the chemotherapy regimen, significant tumour mass reduction was found in the group of patients treated with the taxane compared to the group of breast cancer patients treated with anthracyclines.

In the study by von Minckwitz et al. (16), the comparison between several defined pCRs has shown that the smallest remaining tumour in breast and lymph nodes correlated with the best survival rate. These, as well as other authors (17,18), have suggested that pCR can serve as a model of the achieved benefits of a chemotherapy regimen compared to another regimen.

Influenced by the hypothesis of Goldie Coldman on the use of a combination of multiple cytostatics, it was assumed that the percentage of resistant tumour cells is decreased in this manner (13). In multiple non-randomized and randomized studies about neoadjuvant (preoperative, primary or induction) chemotherapy (NACT), the following combination was used: cyclophosphamide, methotrexate and 5-fluorouracil (CMF) / fluorouracil, adriamycin and cytoxan (FAC) / doxorubicin and cyclophosphamide (AC) (8,13). Several comparative clinical studies in the adjuvant and metastatic setting have shown that the efficiency of the anthracyclines regimen shows the highest degree of response (protocol B-18, B27) (8,13,19). The results of meta-analysis of multiple randomized clinical trials conducted by Coupone et al. with adding taxane to anthracycline regimen (2.455 patients) showed that the degree of sparing breast surgery significantly increased at the expense of adding taxanes to the NACT regimen (20). The pCR level was also higher in patients who received NACT with taxanes.

The results of the toxicity analyses of cytotoxicity treatment tested in our study proved to be consistent with literature data (9). Serious side effects grade 3 and grade 4 were observed neither in the control nor in the study group.

Anthracyclines are among the most effective cytotoxic drugs developed for the treatment of breast cancer but also among the most toxic drugs ever developed (21,22). They induce nausea, as evidenced by the results of this study. Adding taxanes in neoadjuvant therapy of locally advanced breast cancer causes intense vomiting, which in the early decades was so severe that it required hospitalization and intravenous hydration. The results of this study showed the occurrence of vomiting grade 1 in 20% of patients in the study group and 16% in the control group, and grade 2 in 46% of patients in the study group and 54% in the control group.

Taxanes are potent myelosuppressive drugs and they increase the rate of febrile neutropenia, especially if administered simultaneously with anthracyclines (23). Taxanes increase the probability of stomatitis, weakness and sensory neuropathy (23). In the study, the frequency of these side effects was not significantly statistically different among chemotherapeutic groups.

Taxane neuropathy may be particularly severe for patients, and data on the expected duration and recovery rate of this complication are limited (23). Neurotoxicity was registered mostly in patients administered with taxane therapy (54%). All side effects in both groups were generally grade 2, without disturbing the quality of life or causing long-term consequences, and they are mostly reversible. By comparing the results in both patient groups, toxic profile is recorded that does not differ between the two groups of patients, regardless of whether the taxanes are sequentially administered, after anthracycline, or simultaneously with anthracycline, except in terms of peripheral neurotoxicity and bone ache. Similar results were also published by other authors (9,16).

Data from the studies BCIRG 001 and GEICAM 9805 show that taxane regimens have a greater negative effect on the quality of life compared to anthracyclines (23,24). These differences in quality of life vanish by the end of neoadjuvant therapy. However, there is no information on the long-term effects of taxane on the quality of life. Future research should investigate whether long-term quality of life depends on the type of neoadjuvant chemotherapy.

In conclusion, application of taxane in neoadjuvant chemotherapeutic treatment of patients with locally advanced breast cancer significantly increases the extent of the objective response compared to treatment with anthracyclines, while at the same time there is no significant increase in toxicity caused by the therapy.

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TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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