

ROZPRAWA DOKTORSKA

Ocena przydatności oznaczenia wybranych markerów wydzielanych przez komórki śródbłonna naczyniowego oraz tkankę tłuszczową jako czynników prognostycznych w grupie pacjentek z pierwotnym rakiem piersi

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INTRODUCTION AND OBJECTIVE: Breast cancer is one of the most serious oncological problems and represents a growing social, economic and health challenge worldwide. Dysfunction of adipose tissue activity and vascular endothelial cells promotes malignant transformation; hence the aim of this study was to evaluate the concentrations of markers produced by endothelial cells (i.e. t-PA, PAI-1, soluble form of P-selectin and E-selectin, vWF) and adipose tissue (leptin, adiponectin) in a group of patients with primary, unilateral breast cancer without distant metastases. Parameters of the fibrinolysis were compared before treatment in patients with cancer and in healthy volunteers. Other markers were evaluated before and after treatment. In addition, correlations between all parameters and clinicopathological indicators and the type of treatment applied were determined. Furthermore, the study also aimed to assess the prognostic value of these parameters in predicting the occurrence of the disease and its recurrence.

MATERIAL AND METHODS: In publication 1, the study included 60 women aged 41-67 years (mean 52.9 years) with primary unilateral luminal A and B breast cancer without distant metastasis (M0) at stage IA-IIB. The median tumour size was 1.6 cm. Seventeen patients (28%) had lymph node metastases (N1). There were 42 cases at TNM stage I (70%) and 18 at TNM stage II (30%). Ten events occurred in the recurrence-free survival analysis, with a median follow-up time of 33 months (recurrence rate of 16.7%). The study also included 45 healthy volunteers (age range 44-68 years) with mammographically confirmed absence of breast cancer. The study assessed t-PA, PAI-1 and the t-PA/PAI-1 and PAI-1/t-PA ratio in both groups. In publications 2 and 3, the study included 70 patients with primary unilateral luminal A and B stage IA-IIB breast cancer without distant metastasis (M0). The median age was 54.5 years,

and the median tumour size was 1.5 cm. There were 48 patients (69%) in the TNM classification of stage T1 breast cancer and 22 patients (31%) in T2. Only 17 (24%) of the 70 patients had metastasis to local lymph nodes. The median follow-up time was 68.5 months. During this study, 11 events occurred, including one distant metastasis and 10 deaths (recurrence rate: 15.71%). **Publication 2** assessed leptin and adiponectin levels before and after treatment. **Publication 3** evaluated the levels of soluble forms of P and E selectin, vWF and LAR before and after treatment.

RESULTS: As a result of statistical analyses, ROC curves were constructed in publication 1 to assess the diagnostic accuracy of fibrinolysis components, and it was noted that only for PAI-1 the diagnostic utility of the test was achieved. A plasma PAI-1 concentration of 33.91 ng/ml (sensitivity 90% and specificity 36%) was determined as the best cut-off value for distinguishing healthy individuals from breast cancer cases. Further analysis was then performed to predict disease recurrence. The highest AUC^{ROC} value was obtained for t-PA concentration. The cut-off point for t-PA concentration was set at 5.3 ng/ml (66% specificity and 70% sensitivity). This value makes it possible to distinguish between patients with and without relapse. In addition, Kaplan-Meier survival curves showed that patients with a pre-treatment t-PA levels higher than 5 ng/ml were more likely to relapse. Disease recurrence in this group of patients occurred in 7 of 28 (25%) patients.

In publication 2, leptin and adiponectin concentrations increased regardless of the treatment regimen used. In addition, using Spearman rank correlation analysis, it was shown that leptin levels before treatment correlated positively with leptin levels after treatment and negatively with adiponectin levels after treatment, and that adiponectin levels before treatment correlated positively with adiponectin levels after treatment. In the next stage of statistical analysis, ROC curves were constructed, and Kaplan-Meier survival analyses were performed. Based on the results of the study, post-treatment leptin concentration was found to be the strongest predictor of relapse. In addition, a post-treatment leptin concentration of 26.88 ng/ml with a sensitivity of 88.9% and specificity of 64.9% was found to be the best cut-off value to distinguish between patients with and without relapse using the maximum value of the Youden index. The final step in the statistical analysis was to determine linear regression models between pre- and post-treatment adipokines and disease-free survival. Regardless of adjusted factors, they showed that higher leptin levels after treatment were correlated with shorter disease progression-free survival.

In the third publication, regardless of the treatment regimen used, LAR and vascular endothelial markers increased after treatment. Pre-treatment markers were found to correlate positively with their post-treatment counterparts using Spearman rank correlation. Furthermore, the associations of LAR and vascular endothelial markers before and after treatment and disease-free survival were determined using linear regression. A higher risk of breast cancer recurrence was associated with lower sP-selectin levels after treatment confirmed by linear regression. In addition, Kaplan-Meier curves were performed to determine overall survival and disease-free period. Patients with post-treatment LAR levels lower than 0.82 had significantly better overall survival (OS) and disease-free survival (DFS) according to the median cut-off. In addition, patients with post-treatment LAR levels below 0.83 showed better OS and DFS than patients with post-treatment LAR levels above 0.83 according to the cut-off point from the ROC curve. Patients with pre-treatment sP-selectin levels lower than 265.05 ng/ml presented a significantly longer disease progression-free period than patients with pre-treatment sP-selectin levels higher than 265.05 ng/ml, according to the median cut-off value. In addition, patients with pre-treatment sP-selectin concentration below 247.40 ng/ml (cut-off point from the ROC curve) had a longer disease-free period.

CONCLUSIONS: It was found that the concentrations of t-PA and PAI-1, sP-selectin before treatment and the concentration of leptin after treatment can serve as both predictive and prognostic markers in early-stage breast cancer. The complementary therapy used, regardless of the treatment regimen chosen, increased the concentrations of markers produced by adipose tissue and vascular endothelium. In addition, increased levels of leptin and LAR after treatment, and sP-selectin both before and after treatment are associated with a worse prognosis in breast cancer patients.