Background: Nowadays, neoadjuvant chemo- and hormone therapy has been widely used for locally advanced breast cancer patients to reduce tumor size. However, the effect of both neoadjuvant therapy (NAT) on metastatic breast cancer remains unknown, particularly in association with apoptotic-pathway. This study aimed to examine the expression alteration of p53-apoptotic pathways genes in advanced breast cancer patients after neoadjuvant chemo- and hormone therapy.

Methods: We collected stage IIIb and IV breast cancer tissues from 46 patients before and after neoadjuvant chemo- (5-fluorouracil, anthracyclines, cyclophosphamides) and hormone (tamoxifen or aromatase inhibitor) therapy. Patients were treated for 6 months prior to tumor resection. The expression profile of p53-pathway genes was
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investigated using Next-Generation Sequencing and Targeted RNA expression p53 panel comprising of 52 genes (TruSeq®, Illumina). The alteration of the p53-pathway gene expression after NAT was analyzed using dependent t-test and correlated with clinical characteristics and patients' overall survival.

Results: In this study, we found that the expression of 7 genes in p53 panel was significantly altered after NAT. Among these 7 genes, 3 apoptosis-inducing genes (ATM, CASP8 and CASP9) were overexpressed, whereas 1 anti-apoptosis genes BIRC5, as well as 2 proliferative genes (CDK1 and PCNA) were under-expressed. Surprisingly, the death-agonist BID gene was significantly underexpressed. No significant difference of these 7 gene expression profiles based on ER, PR and HER2 status, and NAT types. The ATM gene expression alteration was significantly different between stage IIIb and IV groups. Furthermore, we demonstrated that the alteration of PCNA gene expression was significantly correlated with the patients' 3-years survival.

Conclusions: Alteration of six p53-pathway gene expressions after NAT indicates the effectiveness of both chemo- and hormone therapy to suppress tumor proliferation and induce apoptosis in advanced breast cancer prior to mammosurgery. However, the overexpression of BID gene should be considered as an inducer of therapy resistance.

Clinical trial identification: This study has been approved by The Ethics Comittee of Faculty of Medicine, Universitas Indonesia.

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