Editorial

# Glutathione S-transferases (GSTs) polymorphism and taxane (docetaxel) sensitivity in breast cancer

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The neoadjuvant chemotherapy (NAC) has been commonly used in breast cancer treatment, especially for advanced staged patients. NAC lets alteration of inoperable cancer to operable, and reduces the size of tumor eventually allowing mastectomy cases to receive breast conserving surgery (1). Furthermore, recent studies suggested the predictive role of NAC for prognosis. Tumors with pathologic complete response (pCR) to NAC showed a more favorable prognosis than the tumors with no pCR, although its correlation varies among molecular subtypes. Among these subtypes, hormone receptor positive and HER-2 negative tumors (HR+/HER2–) shows about 8.3% (6.7–10.2%) pCR rate, which is the relatively low rate compared to other subtype tumors (2). This reflects the resistance of HR+/HER2– tumors against chemotherapeutic agents and suggests the needs to select HR+/HER2– tumors which are sensitive to chemotherapy for the improvement of NAC effect.

The 21-gene recurrence score (RS) assay (OncotypeDX®; Genomic Health Inc., Redwood City, CA, USA) was developed to discriminate high risk patients from the patients with estrogen receptor (ER) positive and axillary lymph node negative tumors (3). This assay measures relative expression level of major 16 genes (ER: *ESR1*, *PGR*, *BCL2*, *SCUBE2*; proliferation: *Ki67*, *STK15*; Survivin: *CCNB1*, *MYBL2*; other genes: *HER-2*, *GRB7*, *MMP11*, *CTSL2*, *GSTM1*, *CD68*, *BACG1*) compared to five reference genes [*ACTB* (*b-actin*), *GAPDH*, *RPLPO*, *GUS*, *TFRC*] by high-throughput real-time quantitative reverse transcription polymerase chain reaction (QRT-PCR) using RNA extracted from formalin-fixed paraffin-embedded tumor tissue (FPET) blocks (4). Adjuvant chemotherapy gives survival benefit to high risk patients identified by OncotypeDX® (5). Recently, some studies on application of OncotypeDX® to NAC had been conducted (6-8). Pease *et al.* (8) reported that high OncotypeDX® RS was significantly related with pCR and suggested this assay could be a help for selection of suitable NAC candidates.

Glutathione S-transferase mu 1 (GSTM1), one of the major 16 genes for OncotypeDX® assay, plays a key role to protect cells by detoxifying cytotoxic or genotoxic materials. GSTM1 is a member of glutathione S-transferases (GSTs), which are consisted of six subfamilies-GSTA1 (alpha), GSTT1 (theta), GSTP1 (pi), GSTK1 (kappa), and GST (sigma) including GSTM1 (mu) (9). It has been known that GSTM1, GSTA1, GSTT1 and GSTP1 could protect cells and molecules from reactive oxygen stress (10). Some previous studies reported that polymorphism of these enzymes was related with responses to chemotherapy and prognosis in cancer patients (11,12). In breast cancer, polymorphisms of GSTM1 and GSTP1 were significantly associated with chemotherapy response in previous meta-analysis study. Especially, patients with GSTM1-null genotype showed poor responses to chemotherapy and this was dominant in Caucasians (13). However, some studies did not demonstrate significant relationships between these enzymes and chemotherapy response and these discordances were thought to be the result of differences in ethnicity, number of patients, disease stage and etc. (13). Regarding of prognosis, patients with GSTM1-null genotype had a better overall survival and disease-free survival than patients with non-null genotype (14,15). This might indirectly reflect the responsiveness

to chemotherapy according to GSTM1 polymorphism. Polymorphisms of GSTT1 and GSTP1 were also reported to be associated with good prognosis in breast cancer (14,15). In an ovarian cancer, GSTA1 polymorphism (69 C>T) was related with overall survival, tumors with T/T genotype had better survival than those with C/C carriers (16).

Anthracycline is a main drug in breast cancer chemotherapy including NAC. However, recently taxane based chemotherapies are also being adopted as a main chemotherapy regimen in breast cancer treatment due to cardiotoxicity of anthracycline (17). Susceptibility of tumor cells to taxane according to polymorphisms of GST subfamily is not well reported in breast cancer, although, there are many studies on the anthracycline and polymorphism (13). It might be mainly due to the wide utilization of anthracycline by far, owing to its effectiveness on breast cancer. Regarding of the tumor responsiveness to anthracycline based chemotherapy, polymorphisms of GSTP1rs1695 and GSTM1 were reported to be associated with significant response rates. The patients with A allele of GSTP1rs1695 proposed a better response than those with G allele and the patients with GSTM1 polymorphism also had a better response to anthracycline based chemotherapy (13).

This study evaluated the tumor responsiveness to taxane based chemotherapy according to polymorphisms of GST subfamily and identified GSTM1 polymorphism was associated with responsiveness to taxane. This result might suggest that GSTM1 polymorphism could be a predictor of tumor responsiveness not only to anthracycline but also to taxane. Nevertheless, in a previous study by Romero *et al.* (18) there was no effect of GSTs polymorphism on taxane resistance in breast cancer. Considering these contradictory results, further studies would be needed to clarify the relationship between polymorphisms of GST subfamily and taxane response in breast cancer.

Breast cancer is a heterogeneous group of disease with broad spectra of histological classifications and clinical features. Many *in vivo* and *in vitro* studies on breast cancer have been being conducted and breast cancer cell lines are widely used because of its heterogeneity. Breast cancer cell lines are characterized by ER, progesterone receptor (PR), and HER-2 status and classified as follows; luminal A (ER and/or PR+ and HER2–), luminal B (ER and/or PR+ and HER2+), HER-2 positive (ER and PR– and HER2+), and triple negative (ER and PR– and HER2–) subtypes. HER-2 positive and triple negative cell lines show more aggressive biologic features than others (19). In this study, four cell lines, which are representative for each molecular subtype, are used for *in vitro* experiments. MCF-7 for luminal A, BT474 for luminal B, SKBR3 for HER-2 positive, and MDA-MB-231 for triple negative subtype (19). This result depicted that most aggressive cells, MDA-MB-231, expressed all the 4 GST isozymes and the number of expressed GST isoenzyme was related with aggressiveness of cancer cells. In the comparison of taxane resistant MDA-MB-231 cells from normal MDA-MB-231 cells, taxane resistant MDA-MB-231 cells expressed higher levels of 4 GST isozymes than normal one. These results might come from the role of GSTs, which protect cells from cytotoxic or genotoxic materials. Furthermore, this study showed that GSTM1 and GSTA1 depletion increased docetaxel sensitivity in taxane-resistant MDA-MB-231 cells.

In summary, this study manifested that polymorphism of GSTM1 was related with responsiveness to taxane (docetaxel) in HR+ and/or HER2+ breast cancer patients who had been treated with NAC. *In vitro* test, with using breast cancer cell lines, polymorphisms of GSTM1 and GSTA1 were associated with taxane (docetaxel) sensitivity only in MDA-MB-231 cells, which is a triple negative (HR– and HER2–) breast cancer cell. This study is thought to be meaningful to show the responsiveness of breast cancer to taxane according to GSTs polymorphism, although there is a discrepancy in breast cancer subtype between patients result and *in vitro* test results.

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