Commentary

Defining the subset of the patients in whom "*Less is More*" for hormone receptor-positive breast cancer: clinical risk *vs*. genomics risk

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Omitting adjuvant chemotherapy by risk assessments using clinical and genomic signature is a very important topic for patients and clinician because chemotherapy has potentials to be harmful with various reasons. Currently, NCCN recommend to consider 21-gene RT-PCR assay (1) for patients with hormone receptor-positive breast cancer who have tumor beyond 0.5 cm after curative surgery (2). However, this clinical application of multi-gene assay is not enough to be useful with category 2A level of evidence. In addition, high price of the test is preventing it from becoming widely available.

Recently, another clinical trial result to evaluation multi-gene panel assay has been published to predict response to chemotherapy in 12 years since 21-gene RT-PCR assay had been published, 70-gene signature by the TRANSBIG consortium (3). The MINDACT (Microarray in Node-negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) trial reported contradiction in regards to the use of the 70-gene signature in patients with early-stage breast cancer who were deemed to be at high risk for recurrence on the basis of clinicopathological factors. Patients who were classified as high risk according to clinicopathological factors were able to avoid adjuvant chemotherapy on the basis of a low genomic risk by 70-gene signature, which resulted in a rate of survival without distant metastasis that was an average of 1.5% lower than the rate among those who received chemotherapy.

Treatment de-escalation is always deeply difficult decision for clinicians from the scratch even if the evidence is enough. It requires great certainty. For this point of view, the MINDACT trial still needs to be more validated though it shows how a well-coordinated and highly collaborative multinational team can efficiently conduct a potentially practice-changing study (4). In the clinic, these results could allow some doctors and patients to choose to avoid chemotherapy. However, the decision should be carefully considered and individualized according to the patients' own tolerances for toxicity, risks, and uncertainties (5). Compared with 21-gene assay by RT-PCR (Oncotype Dx®), the MINDACT trial included a wider population of breast cancer patients who were node positive and T2 or T3 with higher tumor grade. It would be a strong point for clinical application. However, differentiation between high and low clinical risk patients based on *Adjuvant Online* may weaken the value for adaptation in real world. More importantly, there is concern to be solved whether biologic difference based on expression assay mainly in ER-positive breast cancer could override clinical factors in higher TNM stage (III). Another weakness is that this study population included HER2-positive and triple negative patients even if it only accounted for less than 10% in total, respectively. There is HER2-positive population which was included as low genomic risk (8%) among the patients with high clinical risk, which is main group of interest in this study. Considering *Adjuvant Online* could not reflect HER2-positivity, clinical risk stratification may be assessed incorrectly. Furthermore, there is difference between chemotherapy and no chemotherapy in patients with high clinical risk and low genomic risk in terms

of disease free survival even though there is no significant difference (hazard ratio 0.64, P=0.03) (3).

The bottom line is whether or not there is a real advantage of 70-gene signature over Oncotype Dx® for clinical application, which is the difficulty of latecomers for similar clinical utility.

Recently, the Trial Assigning Individualized Options for Treatment (TAILORx) result has been published, which was designed to further validate and refine the clinical usefulness of the 21-gene assay in a specified low-risk cohort of women with hormone-receptor-positive, HER2-negative, axillary node-negative invasive breast cancer (6). This result showed that those with tumor that had a favorable gene-expression profile had very low rates of recurrence at 5 years with endocrine therapy alone. This result may have a positive effect on the further application of Oncotype Dx® in daily practice. In this regards, the trial result, which is for the patients with high clinical risk but low genomic risk by 70-gene assay, is warranted.

Obviously, recent advent of multi-omic technologies interrogated further the genomic landscapes of breast cancer through next-generation sequencing (NGS) (7,8) since Perou *et al.* has established gene expression profiling of primary breast cancer, led to the identification of at least four intrinsic subtypes, with different molecular and clinical characteristics (9). The genomic landscape of breast cancer has been implemented for treatment decision especially for patients with refractory metastatic breast cancer at this point. Definitely it will affect early breast cancer soon incorporated into microarray based expression assay as 70-gene signature. Above all, this can be considered as an additional tool to decision-making in adjuvant chemotherapy of early breast cancer patients.

In summary, appropriate clinical applications are still open for patients with high clinical risk for validation. In addition, the cost of the test to use in daily clinical practice will also be an important factor.

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Footnote

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