Editorial

Escalating and de-escalating treatments in HR$^+$HER2$^-$ early-stage breast cancer

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Breast cancer is the most common malignancy among women worldwide. More than 70% of women with newly diagnosed early breast cancer present with stage I to II disease. More than half of these patients are hormone receptor (HR) positive, and human epidermal growth factor receptor 2 (HER2) negative. The main treatment strategy for these patients is endocrine therapy. Tamoxifen or aromatase inhibitor alone is adequate for patients with low risk of recurrence. Premenopausal patients with high risk of recurrence are required to undergo ovarian function suppression combined with tamoxifen or an aromatase inhibitor. Several trials have reported that 10-year endocrine therapy can help to extend survival among higher-risk patients.

Last year, emphasis was placed on the improvement of the areas of escalation and de-escalation treatments for early luminal breast cancer patients. Evidence may be drawn from the results from several phase III randomized controlled trials to guide improvements to the clinical application and individualized approaches to care.

Multigene testing

The risk of relapse might be reduced through the addition of adjuvant chemotherapy. However, if all luminal breast cancer patients were to receive adjuvant chemotherapy, those with low risk of recurrence would be over-treated. Clinicopathological characteristics such as age, tumor size, nodal status, the percentage of HR positive cells, and Ki67-index can be used to stratify different prognostic groups. However, these classic features cannot be used to predict the response to chemotherapy. Therefore, it is essential to establish and validate a predictive tool to evaluate the therapeutic effect and guide the use of adjuvant chemotherapy in early luminal breast cancer patients. Based on the results of the Microarray in Node negative Disease may Avoid ChemoTherapy (MINDACT) trial, the Trial Assigning Individualized Options for Treatment (TAILORx), and other trials regarding 28-gene testing, multigene tests can assist the stratification of patients into different risk of recurrence groups and guide the use of adjuvant chemotherapy.

OncotypeDx® (21-gene) test

Based on the results of TAILORx trial (1), the 21-gene test could evaluate the prognosis and inform chemotherapy benefit in women with HR-positive, HER2-negative, axillary node-negative breast cancer. Among all the women with an intermediate risk score (RS; 11–25) enrolled in the trial, endocrine therapy was comparable to chemotherapy plus endocrine therapy in terms of invasive disease-free survival and overall survival. Furthermore, according to the results from RxPONDER trial (2), patients with 1–3 node-positive and RS ≤25 luminal breast cancer can safely avoid chemotherapy. However, menopausal status was shown to be a confounding factor. For premenopausal patients, the results from TAILORx and RxPONDER trials demonstrated the additional benefit of chemotherapy followed by endocrine therapy.

MammaPrint® (70-gene) test

The MINDACT trial (3) explored the clinical application

of 70-gene testing for women at high clinical risk with HR-positive, HER2-negative, T1–2, N0–1, early breast cancer. Based on the results from the MINDACT trial, clinically high-risk patients who are classified as 70-gene low-risk can safely forgo chemotherapy, especially if the patient is postmenopausal.

The proportion of premenopausal patients in the above trials who received ovarian function suppression was small (4). Furthermore, the survival benefit from chemotherapy-induced amenorrhea has not been evaluated. Therefore, the benefit from chemotherapy for perimenopausal patients is not clear.

Based on the results of several prospective validation multi-center, randomized controlled trials, 21-gene and 70-gene tests were strongly recommended in clinical practice in western countries. However, due to the lack of recruitment of Chinese patients in the above trials, sample and data protection issues, cost-effectiveness considerations, and the accessibility of the multigene testing tools, the clinical application of 21-gene and 70-gene tests remains limited in China.

RecurIndex® (28-gene) test

The 28-gene Chinese-based RecurIndex (RI) (5) test is a multigene assay. It can also estimate the recurrence risk and predict the benefit from adjuvant chemotherapy in luminal breast cancer. The RI integrates information from specific recurrence-related genes in Asian patients and classic clinicopathological features. Several trials have validated the clinical utility of RI to predict the 5-year disease-free survival and to guide the use of adjuvant treatment (6). Currently, it is an urgent need to standardize the multigene testing tools and improve the clinical application of precise treatment for early luminal breast cancer.

Molecular targeted therapy

Recent discordant results from adjuvant trials on CDK4/6 inhibitors in early luminal breast cancer have sparked worldwide debate. The monarchE trial (7) demonstrated that the addition of abemaciclib to endocrine therapy in the adjuvant setting significantly reduced the risk of invasive disease recurrence for high-risk HR-positive, HER2-negative breast cancer patients. In contrast, in PALbociclib CoLlaborative Adjuvant Study (PALLAS) trial (8), no benefit from palbociclib was observed for early luminal breast cancer patients.

As shown in *Table 1*, several potential factors have contributed to the different results. The monarchE trial recruited a higher-risk patient population, who may get more benefit from CDK4/6 inhibitors and be more likely to tolerate severe side effects. Another factor is the discontinuation rate between the two trials. The high discontinuation rate (42.4%) of palbociclib in the PALLAS trial may have reduced the apparent survival benefit.

The Penelope B trial (9) enrolled early luminal breast cancer patients with residual disease after neoadjuvant chemotherapy, who had higher risk of recurrence than those in PALLAS trial. Additionally, only 19.5% of patients in Penelope B discontinued palbociclib in the adjuvant setting, which is comparable to that in the monarchE trial. Although it involved a higher-risk patient population and better adherence was reported, the results from Penelope B still showed no benefit from adjuvant palbociclib for the early luminal breast cancer patients.

Therefore, the genuine differences in pharmacological properties between abemaciclib and palbociclib might mainly explain the different results. Abemaciclib showed anti-tumor activity as a single agent in the metastatic setting, which might be further evidence of the higher efficacy of abemaciclib.

The statistically significant benefit of adjuvant abemaciclib for luminal breast cancer patients with high recurrence risk (based on the results of the monarchE trial) is important in clinical practice, thus abemaciclib is approved and recommended in the international guidelines. Further research on predictive biomarkers for adjuvant abemaciclib is necessary to identify patients who might benefit more and for the improvement of personalized medicine.

The results of the OlympiA trial (10) demonstrated that adjuvant olaparib significantly improved the invasive disease-free survival by 42% in the high risk HER2-negative early breast cancer patients with germline BRCA1/2 mutations. The efficacy of adjuvant olaparib sheds light on its clinical utility in luminal breast cancer with germline BRCA1/2 mutations. In the OlympiA trial, the definition of high-risk luminal breast cancer patients is different to that in the monarchE trial, which may identify the higher-risk patient population and maximize survival benefit.

In summary, we have to maintain our focus on the improvement of escalation and de-escalation treatment for HR-positive, HER2-negative early breast cancer patients. It is clinically important for the implementation of the multigene tests to guide to enable certain luminal breast

Table 1 Characteristics comparison of three phase III trials on CDK4/6 inhibitors in the adjuvant setting

Trials	PALLAS	monarchE	PENELOPE-B
Sample size	5,796	5,637	1,250
Enrollment criteria			
Molecular subtype	$HR^+/HER2^-$	$HR^+/HER2^-$	$HR^+/HER2^-$
Clinical stage	II and III	II and III	Early stage
Neoadjuvant therapy	Yes/no	Yes/no	Yes
Non-pCR	Yes/no	Yes/no	Yes
Nodal status	N0/N+	N+	N0/N+
Recurrence risk	High, intermediate, low	High risk	High risk (CPS-EG score)
Treatment	Palbociclib (2 years) + ET *vs.* ET	Abemaciclib (2 years) + ET *vs.* ET	Palbociclib (1 year) + ET *vs.* ET + placebo
Primary end point	iDFS	iDFS	iDFS
Results	23.7 months; 3-year iDFS: 88.2% *vs.* 88.5%; HR: 0.93 (95% CI: 0.76–1.15)	15.5 months; 2-year iDFS: 92.2% *vs.* 88.7%; HR: 0.747 (95% CI: 0.598–0.932) 19.2 months; 2-year iDFS: 92.3% *vs.* 89.3%; HR: 0.713 (95% CI: 0.583–0.871)	42.8 months; 2-year iDFS: 88.3% *vs.* 84.0%; 3-year iDFS: 81.2% *vs.* 77.7%; HR: 0.93 (95% CI: 0.74–1.17)
Discontinuation rate (due to AEs)	42.4% (27.1%)	16.6% (6.2%)	19.5% (5.2%)

HR, hormone receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; CPS-EG, pre-treatment clinical stage (CS) post-treatment pathologic stage (PS), estrogen receptor status (E) and grade (G); ET, endocrine therapy; iDFS, invasive disease-free survival; HR, hazard ratio; AEs, adverse events.

cancer patients to safely avoid chemotherapy. Furthermore, for the high-risk luminal breast cancer patients, CDK4/6 inhibitors and poly-(ADP-ribose) polymerase (PARP) inhibitors have shown significant survival benefit and their use can improve the clinical application of precise treatment. Meanwhile, management of the side effects could improve patients' quality of life and treatment adherence, and should comprise an essential part of the care of breast cancer patients.

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