June 29th 2019
HONG KONG BREAST CANCER FOUNDATION
ANNUAL SCIENTIFIC MEETING 2019

Summary of Session 3

What Genomic Test to Choose for Patients with Early Stage Cancer

Dr Leung Ching Yu, Roland
Specialist in Medical Oncology, Department of Medicine, Queen Mary Hospital

Unmet need

The prognosis for patients with early breast cancer is generally good. Currently, we base the prognosis on clinical pathological features and make recommendations to patients according to their risk of relapse and offer appropriate adjuvant therapies. With the introduction of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual 8th Edition update, the incoopearation of multigene panel test for risk of recurrence offers maximal prognostic information for patients, achieving personalized survival outcomes.[1]

Multigene assay

For HR+, HER2- patients, extra predictive and prognostic information is much needed. Oncotype DX, EndoPredict, Breast Cancer Index, Mammaprint (MMP) and PAM50 Prosigna are five common multigene assays in Hong Kong. In the 8th Edition update, all the tests are incorporated into staging, while disregarding T size, as they give prognostic information on patients' eventual outcome. As long as the score is low using any of those tests, patients are at low risk, irrespective of T size. Molecular information is now incorporated into staging, providing important prognostic information on how to manage patients with early stage breast cancer.

The genomic tests available use multiple genes which are non-clinical pathological parameters. The tests are developed with clinical trials that included premenopausal, postmenopausal women or both. The background in which the tests were developed must be taken into account during the interpretation of test results. The OPTIMA trial tested 300 British premenopausal and postmenopausal patients with Oncotype DX, MammaPrint, Prosigna and IHC4.[2] Results showed that the four tests did not agree with each other, with Kappa percentage barely above 0.5. Within the same tumour, different genomic tests produced different results. The TransATAC study tested postmenopausal women randomised to tamoxifen or anastrazole with Oncotype, MMP, EPClin, BCI, CTS and IHC4.[3] All the tests lost some power of prediction for node-positive disease.

The TAILORx study recruited pre and post menopausal women with node negative breast cancer. Patients with RX score <11 conferred excellent outcome and could be safely spared from adjuvant chemotherapy. In the main study, patients with RX score 11-25 were randomised to endocrine therapy versus chemo-endocrine therapy. It was initially reported that as a whole group, no clear benefit of adding chemotherapy to endocrine therapy was found.[4] In an exploratory analysis of the original TAILORX study, it was hinted that women aged less than 50 with RX score 15-25 derived

clinical benefit from adding chemotherapy. This finding is relevant to premenopausal early breast cancer patients in Hong Kong because this group accounts for a substantial population of breast cancer. As the original Oncotype DX test is independent of pathological features, interactions between Oncotype DX and pathological features were investigated. The updated results in 2019 showed patients with high clinical risk benefited from chemotherapy, and thus clinical risk provides extra information.[5] In patients aged 41-45 and 46-50, more benefit was observed in the group with chemotherapy on top of endocrine therapy. For patients younger than 50, in the group of patients with Recurrence Score of 16-20, patients with high clinical risk benefited from the use of chemotherapy, whereas in the group of patients with Recurrence Score of 21-25, both high-risk and low-risk patients gained extra benefit from the use of chemotherapy. The study postulated that the use of chemotherapy triggered early menopause, and therefore patients derived extra benefits with anti-hormone therapy.

In practice

Breast Cancer Index is the preferred test to predict who benefits from extended endocrine therapy beyond 5 years. Extra 5 years of endocrine therapy may benefit those patients with high risk of recurrence. Oncotype DX, MMP, Prosigna and Endopredict are able to identify HR+ low-risk patients who can be safely treated with endocrine therapy alone and be spared of chemotherapy. Node-positive disease needs some caution due to the power loss shown by TransATAC data. These tests do not agree with each other, thus ordering more than one test is not recommended. There is emerging data about biological difference with younger patients and the complex interaction of chemotherapy and premature menopause with risk reduction for recurrence, which may alter the clinical application of gene test in the future.

Case Study from *Dr Stephanie HY Lau*

Associate Consultant, Department of Surgery, Queen Elizabeth Hospital

A 49-year-old premenopausal woman presented with 2.1-cm invasive ductal carcinoma which was ER+, PR+ and HER2-, with histologic grade 3 and lymph node-negative. An Oncotype Dx test was ordered and the Recurrence Score was 4. Patient was Stage IIA (AJCC 7th edition), however she will be Stage 1 A (AJCC 8th) TAILORx study recommended endocrine therapy alone with average rate of distant recurrence at 9 years of 3%.[4]

A 47-year-old premenopausal woman presented with 1.5-cm invasive ductal carcinoma which was ER+, PR+ and HER2-, with histologic grade 1 and lymph node-negative. Patient had a Recurrence Score of 22. In TAILORx study, patients with a Recurrence Score of 11-25 were randomized to receive adjuvant chemoendocrine therapy or endocrine therapy alone and had an average rate of distant recurrence at 9 years of 5.5% and 5% respectively.[4] Based on results from exploratory subgroup analysis, patients <50 years old with a Recurrence Score of 21-25 could expect an absolute reduction in 9-year distant recurrence risk of 6.5% with chemotherapy. As a result, chemotherapy should be recommended according to the latest results in TAILORx study.[5]

A 61-year-old postmenopausal woman presented with 1.1-cm invasive ductal carcinoma which was ER+, PR+ and HER2-, with histologic grade 2 and lymph node-negative. Without multigene testing, she would have been recommended to receive hormone therapy alone without further testing. Oncotype Dx test was ordered and patient had a Recurrence Score of 35, thus belonged to Arm D (Recurrence Score 26-100) in TAILORx study and was recommended to receive adjuvant chemoendocrine therapy and with an average rate of distant recurrence at 9 years of 13%.[4]

References

1. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR. AJCC Cancer Staging Manual. 8th ed. US: Springer International Publishing; 2018. 1032 p.
2. Bartlett J, Bayani J, Marshall A, Dunn JA, Campbell A, Cunningham C, Sobol MS, Hall PS, Poole CJ, Cameron DA, Earl HM. Comparing breast cancer multiparameter tests in the OPTIMA prelim trial: no test is more equal than the others. JNCI: Journal of the National Cancer Institute. 2016 Sep 1;108(9).
3. Sestak I, Buus R, Cuzick J, Dubsky P, Kronenwett R, Denkert C, Ferree S, Sgroi D, Schnabel C, Baehner FL, Mallon E. Comparison of the performance of 6 prognostic signatures for estrogen receptor–positive breast cancer: a secondary analysis of a randomized clinical trial. JAMA oncology. 2018 Apr 1;4(4):545-53.
4. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, Geyer Jr CE, Dees EC, Goetz MP, Olson Jr JA, Lively T. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. New England Journal of Medicine. 2018 Jul 12;379(2):111-21.
5. Sparano JA, Gray RJ, Ravdin PM, Makower DF, Pritchard KI, Albain KS, Hayes DF, Geyer JC, Dees EC, Goetz MP, Olson JJ. Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. The New England journal of medicine. 2019 Jun;380(25):2395-405.