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Risk prediction in early triple negative breast cancer

Multigene RNA signature signals benefit from intensified chemotherapy for a high risk group

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Triple negative breast cancer is an aggressive subtype of breast cancer characterised by a lack of oestrogen, progesterone, and HER2 receptors which, if present, would guide the use of targeted therapies. This disease lacks validated prospective biomarkers predicting response to treatment and outcomes beyond basic staging information. The traditional mainstay of systemic treatment for triple negative breast cancer has been chemotherapy.

We need to develop methods to guide treatment decisions in an increasingly complex therapeutic landscape in operable triple negative breast cancer. Enhanced understanding of risk of recurrence and sensitivity to treatment, as is the aim of the linked randomised trial by He and colleagues (BCTOP-T-A01) (doi:10.1136/bmj-2024-079603),[1] can inform decisions about who needs intensive treatment and who might be spared therapies with serious and often permanent toxicities.

The BCTOP-T-A01 trial is the first to prospectively validate a multigene tumour RNA signature to guide choice of chemotherapy in patients with early triple negative breast cancer.[1] This gene expression signature is determined by quantitative real time polymerase chain reaction.[2]

He and colleagues' open label trial recruited 336 people with early triple negative breast cancer with a primary tumour size >10 mm, lymph node involvement, or both across seven cancer centres in China from January 2016 to July 2023. The RNA signature was used to stratify tumours for risk. Participants at high risk were randomised to "standard care" with four cycles of postoperative epirubicin and cyclophosphamide followed by docetaxel or to the "intensive" regimen of four cycles of docetaxel, epirubicin, and cyclophosphamide then four cycles of gemcitabine and cisplatin. Participants at low risk were not randomised and received standard treatment.

The disease-free survival rate was significantly better among participants at high risk who received the more intensive regimen with cisplatin and gemcitabine than in those receiving standard care (90.9% *v* 80.6%; hazard ratio 0.51, 95% confidence interval 0.28 to 0.95; P=0.03). The three year overall survival rate was not significantly different (98.2% *v* 91.3%; hazard ratio 0.58, 0.22 to 1.54; P=0.27); with only 18 deaths across both groups, further follow-up is needed. As expected, the intensive chemotherapy carried a higher risk of haematological grade III-IV adverse events.

As validation of the prognostic value of this score, the patients at low risk had a more favourable disease-free and overall survival than did those assessed as being at high risk who received the same chemotherapy. Whether the low risk group would have also benefitted from more intensive treatment remains unknown, so definitively classifying this test as predictive would be premature.

Implications for treatment

In patients with early hormone receptor positive breast cancer, multigene assays such as the Oncotype DX score have been used for many years to anticipate prognosis and, more importantly, to guide use of chemotherapy.[3-5] Several groups have reported prognostic tumour signatures in triple negative breast cancer,[6-10] but none has been shown to predict response to treatment in a prospective study.

He and colleagues should be commended for developing a new risk signature and validating its use for patients at high risk in a prospective clinical trial. Their data may change practice for oncologists using adjuvant epirubicin and cyclophosphamide followed by docetaxel who can incorporate this new diagnostic test into care pathways.

However, the findings may not change management for many oncologists, simply because the control arm, which represented standard care in 2016 when recruitment began, does not reflect modern evidence and practices in much of the world.[11,12] Several landmark trials in recent years have changed the therapeutic paradigm for early triple negative breast cancer. Modern treatment for early disease can now include immunotherapy for high risk cases and adjuvant poly (ADP-ribose) polymerase (PARP) inhibitor therapy for those with a BRCA mutation.[13,14] Carboplatin improves outcomes,[15] and it is increasingly used, including in the widely adopted immunotherapy regimen evaluated in the KEYNOTE-522 trial.[13] Additionally, systemic therapies are now recommended before surgery for most patients with triple negative breast cancer, to help to gauge treatment response and minimise invasive surgical interventions. Reconciling the lessons of BCTOP-T-A01—to add adjuvant cisplatin and gemcitabine for people with high risk cancers—with modern pre-surgical protocols containing platinum and immunotherapy agents is difficult.

The true innovation of this trial lies in its confirmation of the use of a genomic signature to identify a high risk group of patients who benefit from more intensive chemotherapy. How can this risk score be used to improve practice? A validated predictive test could enhance treatment decisions for many patients, perhaps to guide selection of neoadjuvant chemotherapies such as anthracyclines and platinum agents alongside novel treatments. Hopefully this score, and others, will contribute to a future in which

treatment is more personalised, more targeted, and less reliant on conventional cytotoxic chemotherapy for people with this difficult subtype of breast cancer.

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1 Hw M, Jiang Y, Gong Y, etal. Intensive chemotherapy versus standard chemotherapy among patients with high risk, operable, triple negative breast cancer based on integrated mRNA-lncRNA signature (BCTOP-T-A01): randomised, multicentre, phase 3 trial. *BMJ* 2024;387:e079603.

2 Jiang YZ, Liu YR, Xu XE, etal. Transcriptome Analysis of Triple-Negative Breast Cancer Reveals an Integrated mRNA-lncRNA Signature with Predictive and Prognostic Value. *Cancer Res* 2016;76:-14. doi: 10.1158/0008-5472.CAN-15-3284 pmid: 26921339

3 Paik S, Tang G, Shak S, etal. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006;24:-34. doi: 10.1200/JCO.2005.04.7985 pmid: 16720680

4 Albain KS, Barlow WE, Shak S, etalBreast Cancer Intergroup of North America. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol* 2010;11:-65. doi: 10.1016/S1470-2045(09)70314-6 pmid: 20005174

5 Sparano JA, Gray RJ, Makower DF, etal. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med* 2018;379:-21. doi: 10.1056/NEJMoa1804710 pmid: 29860917

6 Kleivi Sahlberg K, Bottai G, Naume B, etal. A serum microRNA signature predicts tumor relapse and survival in triple-negative breast cancer patients. *Clin Cancer Res* 2015;21:-14. doi: 10.1158/1078-0432.CCR-14-2011 pmid: 25547678

7 Sharma P, Barlow WE, Godwin AK, etal. Validation of the DNA Damage Immune Response Signature in Patients With Triple-Negative Breast Cancer From the SWOG 9313c Trial. *J Clin Oncol* 2019;37:-92. doi: 10.1200/JCO.19.00693 pmid: 31657982

8 Supplitt S, Karpinski P, Sasiadek M, etal. The analysis of transcriptomic signature of TNBC—searching for the potential RNA-based predictive biomarkers to determine the chemotherapy sensitivity. *J Appl Genet* 2024.

9 Yuan C, Yuan H, Chen L, Sheng M, Tang W. A novel three-long noncoding RNA risk score system for the prognostic prediction of triple-negative breast cancer. *Biomark Med* 2021;15:-55. doi: 10.2217/bmm-2020-0505 pmid: 33427499

10 Conte B, Brasó-Maristany F, Hernández AR, etal. A 14-gene B-cell immune signature in early-stage triple-negative breast cancer (TNBC): a pooled analysis of seven studies. *EBioMedicine* 2024;102:105043. doi: 10.1016/j.ebiom.2024.105043 pmid: 38447275

11 Loibl S, André F, Bachelot T, etalESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2024;35:-82. doi: 10.1016/j.annonc.2023.11.016 pmid: 38101773

12 Korde LA, Somerfield MR, Hershman DLNeoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer Guideline Expert Panel. Use of Immune Checkpoint Inhibitor Pembrolizumab in the Treatment of High-Risk, Early-Stage Triple-Negative Breast Cancer: ASCO Guideline Rapid Recommendation Update. *J Clin Oncol* 2022;40:-8. doi: 10.1200/JCO.22.00503 pmid: 35417251

13 Schmid P, Cortes J, Pusztai L, etalKEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med* 2020;382:-21. doi: 10.1056/NEJMoa1910549 pmid: 32101663

14 Geyer CE, JrGarber JE, Gelber RD, etalOlympiA Clinical Trial Steering Committee and Investigators. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol* 2022;33:-68. doi: 10.1016/j.annonc.2022.09.159 pmid: 36228963

15 Mason SR, Willson ML, Egger SJ, Beith J, Dear RF, Goodwin A. Platinum-based chemotherapy for early triple-negative breast cancer. *Cochrane Database Syst Rev* 2023;9:CD014805.pmid: 37681577