Commentary
De-escalation of adjuvant chemotherapy for HER2 negative breast cancer
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In The Lancet Regional Health - Western Pacific Dr Yu and colleagues present the results of the randomized phase 3 non-inferiority MASTER trial, evaluating an anthracycline-free regimen comprising 6 cycles of 3-weekly docetaxel (75mg/m2) and cyclophosphamide (600mg/m2; TC6) compared to two sequential anthracycline-taxane regimens, in women with clinically high risk, HER2 negative early breast cancer, defined by pT1-3 with involved lymph nodes, or T2-3NO with at least one additional risk factor (Grade 2-3, lymphovascular invasion, age ≤ 35, ER/PgR negative) [1].

The study recruited 1663 patients between June 2010 and June 2017 to receive TC6, EC-P: 4 cycles of Epirubicin (90mg/m2) and Cyclophosphamide (600mg/m2) followed by 12x weekly paclitaxel (80mg/m2) or a shorter sequential regimen, CEF-T, comprising 5-FU (500mg/m2), epirubicin (50mg/m2) and cyclophosphamide (500mg/m2) followed by 3 cycles of docetaxel (100mg/m2). Of note, TC6 has never demonstrated superiority over TC4, a key question which will be answered by the CLOVER trial (NCT03926091).

The primary endpoint was disease-free survival (DFS), designed with an unusually generous 4.5% non-inferiority margin at 5 years, corresponding to a hazard ratio (HR) of 1.44 for TC6 compared to EC-P, with a hierarchical design allowing subsequent comparison of CEF-T to EC-T.

After a median follow-up of 5.5 years, 5-year DFS was 85.0% for TC6 and 85.9% for EC-P, HR 1.05, 90% confidence interval (CI) 0.79-1.39 confirming statistical non-inferiority, p=0.048. Similarly, the second comparison confirmed statistical non-inferiority of CEF-T (5-year DFS 85.1% versus 85.9% with EC-P, HR 0.99, 95%CI 0.75-1.30, p=0.045). Sub-group analysis suggested inferiority of TC6 in patients with triple negative breast cancer (HR1.76, 90% CI 0.68-4.52), and, although this sub-group was small (n=81), the authors appropriately confined their non-inferiority conclusions to ER-positive, HER2 negative disease. All regimens were well-tolerated, with very low rates of cardiac toxicity and a single case of therapy-related AML (tAML) reported with EC-P (0.2%), likely a function of the modest sample size and relatively short duration of follow-up.

Due to the era that MASTER was designed in, dose dense regimens were not used as the comparator, arguably impacting on the study results given the known improvement in 10-year freedom from recurrence and breast cancer mortality [2]. Furthermore, although 5-FU containing regimens remain in clinical practice, many oncologists abandoned 5-FU following demonstration of no benefit but increased toxicity in the Gruppo Italiano Mamella study [3] while this study was still accruing patients.

All attempts to find an adjuvant regimen which avoids the potential cardiotoxicity and risk of tAML/myelodysplasia associated with anthracyclines, without compromising efficacy are to be applauded. One of the earliest studies to demonstrate this possibility was a direct comparison of AC4 to TC4, which reported superiority of the non-anthracycline regimen for 5-year DFS (85% versus 80%, HR 0.67, 95% CI 0.50-0.94, p=0.015) in patients with resected stage 1-3 disease of all subtypes [4].

For node negative breast cancer, the CALGB 40101 study demonstrated that 4 cycles of AC was as good as 6 cycles (4-year recurrence-free survival (RFS) 91.8% with AC4 versus 90.9% with AC6, HR 1.03, 95% CI 0.84-1.28), and that 4 (or 6) cycles of paclitaxel monotherapy was a less effective, albeit better tolerated option; 5-year RFS 88% versus 91% with AC, HR 1.26, failing to meet non-inferiority [5,6]. However, in node positive disease, sequential anthracycline-taxane regimens had superseded AC4 alone following significant DFS benefit reported from adding 4 cycles of paclitaxel [7,8]. The MASTER trial includes this high-risk population and its results are in conflict to the much larger ABC trials, which reported that TC6 was not non-inferior to sequential anthracycline-taxane (TaxAC) regimens at the interim analysis after 334 events, using a more conventional non-inferiority definition of a ≥2% dif-

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ference in 5-year invasive DFS, or HR<1.18 [9]. Whilst it is possible that the statistical design alone explains the differing results, it must be noted that the ABC trials enrolled significantly more patients with ER-negative and grade 3 cancers than MASTER and reported similar inferiority of TC6 to sequential anthracycline-taxane in the women with ER-negative disease (HR 1.42, 95% CI 1.04-19.4). Furthermore, the ABC trials required a high-risk Recurrence Score for women with node negative ER-positive cancers whose tumours were not grade 3, which was not required in MASTER. It should also be noted that the Rx-PONDER trial recently demonstrated that post-menopausal women with N1 disease and a low recurrence score can be spared adjuvant chemotherapy [10], therefore it is likely that some node-positive women in both studies did not require chemotherapy at all.

In conclusion, this study adds to the body of evidence that anthracycline-free regimens such as TC can be safely utilized in women with HER2 negative breast cancer who require adjuvant chemotherapy but are unsuitable to receive an anthracycline. However, in the context of the studies discussed above, these results are insufficient to recommend TC6 as a standard regimen; especially given the current absence of data demonstrating that TC6 has any benefit over TC4.

Declaration of Competing Interest

AO receives research funding from Pfizer and Roche; personal fee from Seagen and Pfizer; fees from Astra Zeneca/Daiichi-Sankyo and Leo Pharmaceuticals for attending conference; and fees for Seagen and Roche for participation on a Data Safety Monitoring Board or Advisory Board. MP receives personal fees from Lilly, Roche, Pfizer, Exact sciences, Novartis, and veracyte; fees from Lilly for attending meeting; fees from Lilly, veracyte, and Exact science for participation on a Data Safety Monitoring Board or Advisory Board.

References

[1] Yu, K., Liu, X., Chen, L., Mo, M. et al. Anthracycline-free or Short-term Regimen as Adjuvant Chemotherapy for Operable Breast Cancer: A Phase III Randomized Non-Inferiority Trial. The Lancet Regional Health – Western Pacific. DOI:10.1016/j.laneprw.2021.100158.
[2] (EBCTCG), E. B. C. T. C. G. G. Decreasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37,298 women with early breast cancer in 26 randomised trials. Lancet Apr 2019;393(10179):1440–52 n.
[3] DEL MASTRO L, DE PLACIDO S, BRUZZI P, DE LAURENTIIS M, et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. Lancet May 2015;385(9980):1863–72 n.
[4] JONES SE, SAVIN MA, HOLMES FA, O’SHAUGHNESSY JA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol Dec 2006;24(34):5381–7 n.
[5] SHULMAN LN, BERRY DA, CIRRINCONTE CT, BECKER HP, et al. Comparison of doxorubicin and cyclophosphamide versus single-agent paclitaxel as adjuvant therapy for breast cancer in women with 0 to 3 positive axillary nodes: CALGB 40101 (Alliance). J Clin Oncol Aug 2014;32(22):2311–17 n.
[6] SHULMAN LN, CIRRINCONTE CT, BERRY DA, BECKER HP, et al. Six cycles of doxorubicin and cyclophosphamide or Paclitaxel are not superior to four cycles as adjuvant chemotherapy for breast cancer in women with zero to three positive axillary nodes: Cancer and Leukemia Group B 40101. J Clin Oncol Nov 2012;30(33):4071–6 n.
[7] HENDERSON IC, BERRY DA, DEMETRI GD, CIRRINCONTE CT, et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol Mar 2003;21(6):976–83 n.
[8] MAMOUNAS EP, BRYANT J, LEMBERSKY B, FEHRENBACKER L, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol Jun 2005;23(16):3586–96 n.
[9] BLUM JL, FLYNN PJ, YOTHERS G, ASMAR L, et al. Anthracyclines in Early Breast Cancer: The ABC Trials-USOR 06-090, NSABP B-46-1/USOR 07132, and NSABP B-49 (NIRG Oncology). J Clin Oncol Aug 2017;35(23):2647–55 n.
[10] KALINSKY, K.; BARLOW, W.E.; MERIC-BERNSTAM, F.; GGRALOW, J.R. et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPONDER). SABCS20-GS3-00, Dec 2020.