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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/m^2) and cyclophosphamide (600mg/m^2; TC_6) 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 T2-3N0 with at least one additional risk factor (Grade 2-3, lymphovascular invasion, age $\leq$ 35, ER/PgR negative) [1].

The study recruited 1663 patients between June 2010 and June 2017 to receive TC_6, EC-P: 4 cycles of Epirubicin (90mg/m^2) and Cyclophosphamide (600mg/m^2) followed by 12x weekly paclitaxel (80mg/m^2) or a shorter sequential regimen, CEF-T, comprising 5-FU (500mg/m^2), epirubicin (50mg/m^2) and cyclophosphamide (500mg/m^2) followed by 3 cycles of docetaxel (100mg/m^2). Of note, TC_6 has never demonstrated superiority over TC_4, 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 TC_6 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 TC_6 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 TC_6 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 AC_4 to TC_4, 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 CALBG 40101 study demonstrated that 4 cycles of AC was as good as 6 cycles (4-year recurrence-free survival (RFS) 91.8% with AC_4 versus 90.9% with AC_6, 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 AC_4 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 TC_6 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 $\geq$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 TC_6 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 TC_6 as a standard regimen; especially given the current absence of data demonstrating that TC_6 has any benefit overTC_4.

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 Lily, Roche, Pfizer, Exact sciences, Novartis, and veracyte; fees from Lily for attending meeting; fees from LiLy, veracyte, and Exact science for participation on a Data Safety Monitoring Board or Advisory Board.

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