The potential role of cyclooxygenase-2 (COX-2) during early breast cancer therapy

Neoadjuvant clinical trials have reported objective clinical response rates as high as 49%–94% and pathological complete response (pCR) rates, defined as absence of residual invasive or in situ disease, ranging between 4% and 34% [1]. An indication that pCR may be deemed a surrogate for outcome in this setting came from short follow-up data (5 years), where pCR predicted longer disease-free survival (DFS) \( (P < 0.001) \) [2]. A pCR of 13% was derived from the large National Surgical Adjuvant Breast and Bowel Project (NSABP-B18) which recruited 1523 patients and used neoadjuvant doxorubicin cyclosphosphamide (AC), while pCR of 26%–34% was recently reported from neoadjuvant studies using taxanes [3]. The NSABP-B27 trial recruited 2411 women and compared neoadjuvant AC versus AC followed by docetaxel (T), and despite a clear improvement in response rates (40% complete clinical response and 13% pCR with AC versus 64% complete clinical response and 26% pCR with AC + T), no overall survival benefit was noted. A Royal Marsden series \( (n = 995) \) with the follow-up of 15 years equally failed to demonstrate a survival benefit from the use of neoadjuvant chemotherapy [4].

One could conclude that the pCR end point may be available too late in the course of the neoadjuvant treatment, as it is only derived at the time of surgery hence is not a robust enough surrogate marker of DFS and overall survival. Similarly, exhaustive efforts in evaluating predictive value of baseline markers such as levels of estrogen receptor alpha (ER-\( \alpha \)), progesterone receptor (PgR), Her2 and tumour grade have reiterated what we have learnt from the adjuvant setting in terms of the value, and these tumour characteristics could be expected to have in predicting response to neoadjuvant chemotherapy. High tumour grade and ER\( \alpha \)-negative status predict for increased chemosensitivity, while Her2 positivity indicates favourable response to anthracycline-based neoadjuvant regimens and also proposes inclusion of neoadjuvant anti-Her2 therapy, though not in combination with anthracyclines due to cardiac risk [5–7]. Epidermal growth factor receptor (EGFR)-positive tumours are considered candidates for neoadjuvant anti-EGFR inhibitors (gefitinib, lapatinib) in the trial setting [7], while advanced hormone-responsive disease is also being targeted by neoadjuvant tamoxifen or aromatase inhibitors in neoadjuvant clinical trials (P024 comparing neoadjuvant effects of letrozole versus tamoxifen in 324 women and the IMPACT trial comparing neoadjuvant tamoxifen, anastrazol and combination in 330 women) [8, 9]. Still, overall survival benefit of neoadjuvant approaches remains elusive.

Therefore, in the era of molecular oncodiagnostics, the short window neoadjuvant trials are being viewed as a therapeutic opportunity to evaluate the benefit of new treatment regimens and tailor therapy to the biological characteristics of the tumours, particularly, as they provide a unique access to repeated tissue sampling. Routine practice entails and most studies follow, obtaining a diagnostic-core biopsy, followed by surgical resection sample. Obtaining multiple intermediate samples during the course of neoadjuvant chemotherapy potentially allows for detailed analysis of serial changes in expression of molecular markers within tumours occurring during and as a consequence of applied neoadjuvant treatment regimen.

In a study reported in this edition of the journal, Chua et al. [10] report for the first time that the neoadjuvant chemotherapy-induced reduction in cyclooxygenase-2 (COX-2) tumour expression levels is noted predominantly among responders and is associated with favourable DFS. The authors analysed 100 East Asian females with locally advanced or metastatic breast cancer in a prospective single-centre open-label randomised phase II study. Participants were received either six cycles of doxorubicin (A) and T in tri-weekly cycles and in T-A-T-A-T-A or an A-T-A-T-A-T sequence. Core biopsies were taken from approximately the same region of the tumour, with sampling carried out four times: before neoadjuvant treatment, 3 weeks after the first cycle, 3 weeks after the second cycle and at treatment completion/withdrawal from study. COX-2, ER-\( \alpha \), PgR, Her2, EGFR, p53 and Ki-67 were analysed. The objective clinical response rate achieved was 83.6%, within the previously reported range. No significant changes in ER-\( \alpha \), PgR, Her2, EGFR, p53 or Ki-67 in repeated samples were noted. However, COX-2 appeared as a promising new marker whose expression levels do fluctuate with neoadjuvant chemotherapy and may indeed be predictive of survival benefit. Of the enrolled patients, 65% had COX-2-expressing tumours at baseline, and COX-2 expression correlated with high grade and tumour size, as previously reported. A progressive downward trend in COX-2 expression was observed with increasing cycles of chemotherapy, more precisely between the third and the last cycle. This was statistically significant in clinical responders \( (P < 0.001) \) and although nonsignificant, there may possibly be a benefit for tumours switching from COX-2 positivity to COX-2 negative status \( (P = 0.173) \). In predefined subset analyses, this impact seemed to be most prominent and derived from the ER\( \alpha \)-positive subset of patients, where reduction of COX-2 levels during neoadjuvant chemotherapy was a significant predictor of increased DFS (52.0 months) compared with ER\( \alpha \)-positive
tumours where neoadjuvant chemotherapy had no effect of COX-2 levels (27.0 months; P < 0.002).

The authors conclude that since COX-2 emerged as a potential predictor of neoadjuvant chemotherapy benefit in advanced breast cancer, combination regimens with COX-2 inhibitors may yield even more favourable survival results, particularly, for the patients where neoadjuvant chemotherapy does not reduce COX-2 levels. Furthermore, they emphasise the importance of the underlying ER-\(\alpha\)/COX-2 interaction and propose that advanced ER\(\alpha\)-positive disease where COX-2 is expressed would benefit from the introduction of COX-2 inhibitors into the chemotherapy and/or hormonal therapy neoadjuvant regimens.

In aggregate, Chuah et al. highlight the importance of sequential sampling in gaining improved understanding of temporal changes of molecular mechanisms of response to neoadjuvant treatment.

COX-2 is a prominent feature of premalignant and malignant neoplasms [11]. Chuah et al. found COX-2 expression in 65% of patients, in line with previous reports where COX-2 positivity is detected in ~40% of breast cancers, frequencies ranging from 17% to 84% [12]. The fact that similar characteristics have been observed in a much larger European groups of patients, and the data of Chuah et al., reinforces the proposition that ‘Western’ data merit validation with Asian cohorts, and vice versa. It would be informative to demonstrate that these data are robust and reproducible in a larger patient cohort, as well as to investigate a correlation of COX-2 levels from serial biopsies in the neoadjuvant setting with the pathological response rate and not only clinical response, as was the case here. One must keep in mind the pitfalls such as standardised tissue handling and processing, which can influence the readouts of molecular biomarkers.

The mechanism of COX-2 up-regulation in breast cancer could result from constitutive active Ras/MAPK and Akt/PKB activation. COX-2 catalyses the initial step in prostaglandin formation (PGE2), influencing breast cancer apoptosis, angiogenesis and invasion [13]. COX-2-mediated PGE2 production elevates aromatase activity and links the relevance of COX-2 in promotion of ER\(\alpha\)-positive breast cancer growth, particularly, in postmenopausal women [14]. Additionally, the fact that decrease of COX-2 infers better survival potentially implicates the importance of COX-2-mediated ‘inflammogenesis of cancer’ in influencing response to neoadjuvant chemotherapy [15].

The importance of COX-2 as a target with oncogenic potential is emerging from studies investigating long-term use of aspirin that targets COX-2, in prevention of cancer development. Rothwell et al. recently reported 20-year follow-up from randomised trials of daily aspirin versus no aspirin use with mean duration of scheduled trial treatment of 24 years, assessing the effect of aspirin on the cancer incidence and mortality. They show that daily aspirin intake reduced the risk of death due to cancer by ~20%, and these results were applicable across different cancer types although the benefits in colon cancer may for example result from gastrointestinal complications leading to increased investigations and earlier diagnosis [16].

Chan et al. followed up 82,911 women and 47,363 men and found 636 incident cases of colorectal cancer among users and nonusers of aspirin that were available for analysis of COX-2 expression. Among these 636 tumours, 67% were COX-2 positive. They further demonstrated that the nonselective COX-2 inhibitor aspirin reduced the risk of colorectal cancers that specifically overexpress COX-2, doing so by depleting COX-2-expressing cancer cells. By inference, aspirin intake had no effect on the risk of colorectal cancers with weak or absent COX-2 [17]. Unlike Rothwell et al. where a similar reduction of colon cancer incidence was observed with the lower (75 mg/daily) and higher (300–1200 mg/daily) doses of aspirin, this study found that a reduction of the risk of COX-2-positive tumours was found with increasing aspirin dose and increasing duration of use. Importantly, a prospective cohort study of 1279 men and women diagnosed with stage I, II or III colorectal cancer, and a median follow-up of 11.8 years demonstrated that regular aspirin use after the diagnosis of colorectal cancer was associated with lower risk of colorectal cancer-specific and overall mortality, especially, among individuals with tumours that overexpress COX-2 [18]. A randomised controlled presurgical study of the COX-2 inhibitor (celecoxib) monotherapy did not alter markers of biological response (ER-\(\alpha\), PgR or even COX-2 levels) but did demonstrate a reduction of Ki-67 levels in ER-\(\alpha\)-positive patients [14], corroborating the conclusion of Chuah et al. [10]. Furthermore, co-administration of celecoxib with chemotherapy significantly lowered the threshold of sensitivity to chemotherapy further suggesting that introduction of COX-2 inhibitors to neoadjuvant therapy protocols may not only increase survival but also enable dose reduction of cytotoxic agents hence facilitating evasion of chemoinduced acute and late toxic side-effects [19].

In the case of COX-2-targeted therapies, data from the neoadjuvant setting will inform the results of adjuvant clinical trials ongoing with COX-2 inhibitors, such as the REACT trial in Europe (phase III multicentre double-blinded celecoxib versus placebo following adjuvant chemotherapy) where hormonal therapy is given alongside the selective COX-2 inhibitor celecoxib or placebo in the ER\(\alpha\)-positive subset of patients in the trial [20]. Aberrant induction of COX-2 appears to play a relevant role in carcinogenesis, and investigating its role in the neoadjuvant setting provides an ideal setting for its study.

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The authors declare no conflict of interest.

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