Editorial

Annals of Oncology 16: 1407–1410, 2005
doi:10.1093/annonc/mdi288
Published online 2 August 2005

'Small' randomised neo-adjuvant chemotherapy trials in breast cancer reporting on pathological response: more harm than good?

The main clinical advantage of neo-adjuvant chemotherapy in operable breast cancer is that it has improved the ability to perform breast-conserving therapy. In addition, it can be considered as an ideal model for studying chemosensitivity *in vivo* [1]. Observations from early studies, both single arm phase II studies and those randomising pre-operative systemic therapy against post-operative adjuvant therapy, have confirmed that those women whose tumours have a pathological complete response to neo-adjuvant chemotherapy have the best long-term outcome, and this remains true after multivariate analysis [2, 3]. Therefore, pathological complete response is now considered as a surrogate for survival and since the mid-1990s, clinicians have made this a primary or secondary end point in randomised trials of pre-operative chemotherapy. It has even been suggested that regimens achieving a higher proportion of patients in pathological complete response should then be used in the adjuvant setting as they must give a survival improvement on older treatments. The TOPIC 2 trial, which is published in this issue of *Annals of Oncology*, is one of these randomised trials, looking to improve upon a conventional adjuvant regimen [4]. We felt that it would be interesting, therefore, to put this trial into perspective with other small randomised neo-adjuvant chemotherapy trials that have also reported pathological complete response results (Table 1) [5–16].

The TOPIC 2 trial randomised 451 patients with large operable breast cancer to receive either six cycles of doxorubicin and cyclophosphamide (AC) in the standard arm or six cycles of vinorelbine and epirubicin (VE) in the experimental arm, to be followed by locoregional treatment. The authors report in this issue the first results on response and tolerability, and the bottom line is that there is no difference in clinical response or pathological response between the two arms, although the toxicity profiles are slightly different (more alopecia and nausea with AC and more thrombophlebitis and neuropathy with VE). The primary end point of the TOPIC 2 trial was to detect an improvement in the 5-year relapse-free survival from 50% in the standard arm to 65% in the experimental arm. This assumption is, in the light of current adjuvant chemotherapy results, extremely optimistic. A more realistic design would have been to make the pathological complete response rate the primary end point (in this trial it was a secondary end point). In this report there is no difference in the pathological response rates between the two treatment arms, which therefore makes it very unlikely that a clinically relevant or statistically significant disease-free survival difference will emerge when the final analysis is performed after the planned 190 events.

Has this or any of the other 'small' randomised neo-adjuvant chemotherapy trials influenced clinical practice? The short answer should be 'no, they cannot', since most of these trials have yet to report on survival. However, in reality they have wrongly changed practice in many centres despite the fact that these data are not sufficient to be considered level 1 evidence. The best example is what happened as a consequence of the 'Aberdeen' trial, where some practices were changed as a consequence of data from 97 patients randomised to either continue with anthracycline chemotherapy or switch to a taxane [5]. Those patients switched to the taxane had a higher pathological complete response, which appeared to translate to a survival advantage [6]. Any change in practice is clearly not the fault of the Aberdeen breast group, whose design was novel, looking to further improve the outcome for those women whose tumours were sensitive to the first chemotherapy; but a trial with only 97 randomised patients, and no independent review of the pathological response, should have been seen by the oncology community as only sufficient for hypothesis generating. Similar comments apply for any other change of practice based on any of the trials in Table 1, which report differences in pathological complete response between two chemotherapy arms or regimens.

The main issue is the uncertain biological significance of a pathological complete response. Is it a pure prognostic factor for a good outcome with systemic chemotherapy, or a predictive factor representing a biological parameter influenced by the specific treatment and not just the intrinsic biology of the tumour? If pathological complete response is a predictive factor, an increase of the pathological complete response rate in a randomised trial comparing two chemotherapy regimens should translate into a survival advantage. This is the hypothesis behind much contemporary thinking in the breast oncology community, but has it been demonstrated in a prospective clinical trial? The answer is 'not yet', and the recent results of National Surgical Adjuvant Breast and Bowel Project Protocol B-27 suggest that it may not be true [17]. Early results of this trial have shown that the pathological complete response rate was almost doubled in women treated with neo-adjuvant doxorubicin AC followed by docetaxel compared with AC alone (26.1% versus 13.7%) [18]. In December 2004 the outcome data from this trial were presented at the San Antonio Breast Cancer Symposium with a median follow-up of 69 months, and failed to demonstrate any survival difference (relapse-free, distant disease-free or overall survival) between the treatment arms [17]. A possible

Table 1. Pathological response rates in 'small' randomised trials comparing different regimens of neo-adjuvant chemotherapy

Study group [reference]	n [a]	Treatment A	Treatment B	pCR%[b]	DFS%
Aberdeen [5, 6]	97 (162)	CVAP ×8	CVAP ×4 → D ×4	16/34 ($P = 0.04$)	5-year DFS 78/93 ($P = 0.04$) (md fu 65 m)
ACCOG [7]	363	AC ×6 q3w	AD ×6 q3w	24/21 ($P = 0.61$)	No difference ($P = 0.17$) (md fu 32 m)
AGO [8]	475 (631)	EP ×4 q3w	E ×3 → P ×3 q2w	10/18 ($P = 0.03$)	NR
ETNA [9]	191	AP ×4	AP ×6	17/30	NR
French study [10]	200	AC ×4	AP ×4	10/16	No difference (md fu 31 m)
				6/8[c]	
GEPARDO [11]	250	AD ×4 q2w	AD ×4 q2w + Tam	12/12	NR
GEPARDUO [12]	913[d]	AD ×4 q2w	AC ×4 → D ×4 q3w	7/14 ($P < 0.001$)	NR
GIREC [13]	90	FEC100 ×6	ED ×6	24/24	NR
MDA [14]	174	CAF ×4	P ×4	16/8 ($P =$ NS)	2-year DFS 89/94 ($P = 0.44$)
MDA [15]	258	P ×4 q3w → CAF ×4	Weekly P ×12 → CAF ×4	14/29 ($P < 0.01$)	NR
TOPIC [16]	426	AC ×6	ECisF ×6	25/24	NR
TOPIC 2 [4]	451	AC ×6	VE ×6	12/12	NR

[a] n, number of patients randomised.

[b] Different pCR definitions were used.

[c] The pCR% determined by study centre pathologists were 10 and 16 in the AC and AP treatment arms, respectively; these rates determined by an independent expert review were 6 and 8, respectively.

[d] With 913 patients, the inclusion of this study in the group of 'small' randomised trials is debatable. Of note, the enrolment in this study ended after an interim analysis assessing the pCR% of the first 395 patients included in the trial (at that point 913 patients were already included). This analysis showed a statistically significant higher pCR% for patients treated in arm B.

pCR, pathological complete response; DFS, disease-free survival; md fu, median follow-up; m, months; NR, not reported; CVAP, cyclophosphamide, vincristine, doxorubicin, prednisolone; D, docetaxel; AC, doxorubicin, cyclophosphamide; AD, doxorubicin, docetaxel; EP, epirubicin, paclitaxel; P, paclitaxel; AP, doxorubicin, paclitaxel; FEC100, fluorouracil, epirubicin, cyclophosphamide; ED, epirubicin, docetaxel; CAF, cyclophosphamide, doxorubicin, fluorouracil; ECisF, epirubicin, cisplatin, infusional fluorouracil; VE, vinorelbine, epirubicin; Tam, tamoxifen; q3w, every 3 weeks; q2w, every 2 weeks; NS, not significant.

explanation for this lack of benefit is that both the treatment duration and the number of chemotherapy cycles were different. A longer duration of chemotherapy may have further reduced the extent of local disease, such that some additional pathological complete responses were identified, but without an impact on the natural history of any micrometastatic disease. The ongoing EORTC 10 994/BIG 00-01 trial is randomising over 1800 patients between two treatments with an equal number of chemotherapy cycles over the same duration (either six cycles of fluorouracil, epirubicin, and cyclophosphamide, or three cycles of docetaxel followed by three cycles of epirubicin plus docetaxel), such that it will inform as to whether a difference (if any) between the pathological complete response rate with treatment A or B will translate into a survival difference.

What can we conclude from these small randomised trials? From a clinician's perspective, it should be acknowledged that these small trials that emphasised pathological complete response rates, but cannot confirm their long-term benefit, may have done more harm than good. This is because, based on these data many clinicians have changed their practice and have exposed their patients to additional, toxic chemotherapy. From the standpoint of clinical research, one is tempted to say that these trials did not meet our expectations. This would imply that there is no more room for such small randomised neo-adjuvant trials looking for pathological complete responses, since any new regimens tested in the neo-adjuvant setting must still be studied only in the context of large phase III trials. However, I think exactly the opposite is true and would like to argue for a structured future for 'small' randomised neo-adjuvant chemotherapy studies.

The first proposal would be to use pathological complete response rate as a mandatory checkpoint, or early stopping rule, when designing or developing a trial comparing two chemotherapy regimens in early breast cancer. In such a design, if there is no difference in pathological complete response rate between the two (or more) treatment arms after inclusion of a few hundred patients, well balanced between the arms for factors predictive of pathological complete response, one could reasonably hypothesise that no survival difference will emerge even after inclusion of several thousands of patients. For a trial aimed at equivalent efficacy but better toxicity we could potentially stop the trial and switch to the better tolerated therapy; for one aimed to improve outcome, it would be back to the drawing board to look for a newer strategy to be tested. It would save money, as large trials are expensive,

save patients toxicity, as new chemotherapy treatments are usually more toxic, and save time, avoiding putting patients into trials very unlikely to change practice. On the other hand, if there is a difference in the rates of pathological complete response, the trial should enter a second phase allowing the inclusion of patients who could receive the chemotherapy treatments being tested in the trial in either the neo-adjuvant or the adjuvant setting. It is of interest to note that none of the trials summarised in Table 1 used this strategy, including those which demonstrated a pathological complete response difference, despite obvious potential implications.

A second suggestion would be to explore new chemotherapy regimens in the subgroup(s) of patients whose tumours are more likely to respond to chemotherapy. Inclusion of patients with little chance of obtaining a pathological complete response could explain the negative or weakly positive results of previously reported trials, since such patients would dilute the overall rate of pathological complete response. Several publications have shown higher pathological complete response rates in tumours not expressing steroid hormone receptors. In a retrospective study of 399 patients treated at the European Institute of Oncology, the pathological response rate of negative estrogen and progesterone receptor expression compared with those having some expression was 33% and 7.5%, respectively [19]. Other studies reported similar results [12, 18, 20]. Moreover, concentrating on a more homogeneous group of tumours (such as those negative for both the estrogen and progesterone receptor) could permit identification of factors predictive of response to a specific chemotherapy agent.

The third proposal, perhaps the most challenging, is the integration of so called 'targeted therapies' in the neo-adjuvant model. To illustrate this, we will concentrate on one group of these targeted therapies, the anti-ErbB receptor family agents. Taking the precedent of trastuzumab, these new molecules could be used either as monotherapy, in combination with different anti-receptor therapies or other molecular targeted therapies (downstream signalling transduction inhibitors or antiangiogenic molecules), or more simply in combination with conventional chemotherapy. A recently published randomised study gives a good example of the combined approach with chemotherapy [21]. Patients with HER-2 positive large operable breast cancers were randomly assigned to either four cycles of paclitaxel followed by four cycles of fluorouracil, epirubicin and cyclophosphamide, or to the same chemotherapy with concomitant weekly trastuzumab. The primary end point was the pathological complete response rate. The trial was closed prematurely after inclusion of 42 patients (out of 164 planned) because of a more than two-fold increase in the pathological complete response rate favouring patients who received the combined treatment (25% versus 66.7%; $P = 0.02$). The main message from this trial is that the neo-adjuvant model could rapidly test the synergy between chemotherapy and a specific targeted therapy agent, trastuzumab, and that this observation deserves further evaluation. However, this trial does not tell us that the standard neo-adjuvant treatment of HER-2 tumours should be chemotherapy and concomitant trastuzumab for at least two reasons. First, however encouraging the improvement in pathological complete response rate, it remains a small trial, and any unintentional imbalance between the two arms in factors (perhaps hitherto unrecognised) that predict for sensitivity to the chemotherapy could have given rise to a similar difference. Secondly, the results of both the HERA trial and the US joint analysis presented at the ASCO meeting this year show very similar reductions of the relative risk of relapse [22]. The difference between the trials is that in the HERA trial, trastuzumab was delivered after completion of adjuvant or neo-adjuvant chemotherapy, whereas the joint US trial analysis related to patients given trastuzumab concomitantly with taxol chemotherapy. Therefore, although the neo-adjuvant study appears to support the addition of trastuzumab to the adjuvant treatment programme, it cannot confirm when it should be given in terms of either before surgery or concomitantly with the chemotherapy. However, all is not rosy in the garden of combining anti-ErbB agents and chemotherapy. Baselga and Arteaga [23] recently emphasised in a review that the correlation between preclinical models and clinical results is good with anti-HER-2 therapies but very poor with anti-EGFR agents, as exemplified by four negative phase III studies in non-small-cell lung cancers. Had combinations of anti-EGFR therapies and conventional agents been first tested in neo-adjuvant trials, with the clinical and pathological tumour response analysed *in vivo* along with biomarkers studies on repeated core biopsies (concomitantly with pharmacokinetic studies), then perhaps the large phase III studies might not have been needed. Although such studies may be more difficult to perform in lung cancer, we would have no excuse not to perform these in breast cancer.

Based on the three proposals mentioned above, an 'ideal study' would commence with a phase I design followed by a randomised phase II and only proceed to a phase III if there was sufficient evidence to support such a large study. The phase I would define the maximum tolerated dose and the optimal biological dose. The aim of the subsequent randomised phase II should be to detect an increase in pathological complete response rate with the novel therapy. If confirmed, the study would extend into a phase III trial looking for a survival difference. If no significant difference in pathological complete response rates are detected, this information would avoid including several thousand patients in a phase III trial unlikely to lead to a more effective therapy. At the same time, tumour samples taken from both the phase II and phase III studies could be used to identify whether there is a subgroup of patients more likely to respond to the novel treatment. The EORTC Breast Cancer Group is developing such an approach looking to combine a novel anti-Her-2 therapy with a potent single agent drug in breast cancer, docetaxel.

What have we learnt from small randomised trials such as that reported by Chua et al. [4] in this issue? I think it is clear that such studies on their own no longer have a place in the development of better chemotherapy treatments in early breast cancer. However, their basic design, together with parallel

pathological response and marker assessments, has the potential to be a springboard to rapidly test novel combinations (i.e. an anti-ErbB receptor family agent and conventional chemotherapy), which, when shown to be more effective, can be tested for their true adjuvant benefit in a large definitive phase III trial. The report by the TOPIC 2 trialists strongly suggests that its research arm should not be taken forward to a large phase III trial; but we, and our patients, are indebted to them for preventing us running such a large trial that would have been very unlikely to lead to a more effective therapy.

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