Neoadjuvant chemotherapy: what does it take to tAnGo?

Nicholas Zdenkowski[1,2], Nicole McCarthy[3,4]

[1]Australia and New Zealand Breast Cancer Trials Group, NSW, Australia; [2]University of Newcastle, NSW, Australia; [3]ICON Cancer Care Wesley, QLD, Australia; [4]University of Queensland, QLD, Australia

Correspondence to: Dr. Nicholas Zdenkowski, BMed, FRACP. Australia and New Zealand Breast Cancer Trials Group, PO Box 155, HRMC, NSW 2310, Australia. Email: nicholas.zdenkowski@anzbctg.org.

Abstract: Use of additional chemotherapy agents is a time-proven method of achieving an incremental survival gain in early breast cancer. A decade has passed since the publication of trials showing the benefit of adding taxanes to anthracycline-based adjuvant chemotherapy. Neo-tAnGo and the companion tAnGo trial set out to test whether additional benefit could be achieved by adding gemcitabine in the neoadjuvant and adjuvant settings, respectively. Neo-tAnGo also investigated the effect of sequencing paclitaxel either before or after epirubicin and cyclophosphamide (EC). The addition of gemcitabine was not associated with an improvement in pathological complete response (pCR) or survival, consistent with other trials that incorporated gemcitabine into neoadjuvant or adjuvant chemotherapy. Administration of paclitaxel prior to EC resulted in a 5% higher pCR rate compared with the reverse sequence (P=0.03). The pCR difference did not translate into a survival advantage. Neoadjuvant therapy is an important clinical trial platform to assess the effectiveness of new agents in early and locally advanced breast cancer. Early endpoints such as pCR, serial biopsies and imaging can be used to evaluate the activity of new therapies. The link between improvements in pCR and survival in the neoadjuvant setting, and translation of benefit into the adjuvant setting is tantalisingly close - particularly in the triple negative breast cancer and HER2 positive breast cancer subtypes - but the association remains inconsistent. This editorial will contextualise the results of the Neo-tAnGo in the current and future neoadjuvant trial landscape.

Keywords: Breast cancer; neoadjuvant; gemcitabine; paclitaxel; sequencing

Submitted Jun 17, 2014. Accepted for publication Jun 18, 2014.
doi: 10.3978/j.issn.2218-676X.2014.06.11
View this article at: http://dx.doi.org/10.3978/j.issn.2218-676X.2014.06.11

Despite advances in breast cancer treatment, a significant percentage of women with early breast cancer will experience an incurable recurrence of their disease. New drugs which have proven effective in metastatic disease have been successfully incorporated into treatment algorithms for earlier stage disease, as evidenced by the taxanes, aromatase inhibitors and trastuzumab (1-3). Mortality continues to fall, partly as a result of these advances. However, large adjuvant trials in relatively unselected breast cancer patient populations are no longer feasible, primarily due to skyrocketing costs and a greater understanding of the growing number of biological subtypes of breast cancer. Future trials will need to tailor treatment more rationally and more effectively by using subgroup-specific strategies. Much hope has been placed on the use of neoadjuvant therapy as a clinical trial platform as an alternative to adjuvant trials. Neoadjuvant trials make use of the early biological end point of pathological complete response (pCR) rate to help determine the most effective treatment and aim to predict which agents will be associated with a survival advantage in the adjuvant setting.

At the beginning of this century, there was much interest in combining non-cross resistant chemotherapy drugs in an attempt to improve survival rates. In women with metastatic breast cancer, gemcitabine in combination with paclitaxel resulted in a small but significant survival benefit compared with paclitaxel alone (4). It was anticipated that this would translate into a similar survival benefit for women with locally advanced or early breast cancer. Neo-tAnGo is a randomized neoadjuvant trial that used a 2×2 factorial design to compare

pCR and survival rates of preoperative paclitaxel alone or in combination with gemcitabine followed by epirubicin and cyclophosphamide (EC), or the reverse sequencing of the anthracycline first followed by the taxane alone or in combination with gemcitabine (5). Just over 830 women were recruited to this trial between 2005 and 2007. In general this was a high risk cohort: 50% of patients had axillary lymph node involvement; 25% had inflammatory or locally advanced disease; 40% had grade 3 tumors; 27% were HER2 positive and 33% were estrogen receptor (ER) negative. As with many studies of this era, trial inclusion was not dependent on hormone receptor, HER2 or genomic subtype. Neoadjuvant trastuzumab was not used for HER2 positive patients in this trial. Disappointingly the pCR rate was the same (17%) in both the gemcitabine and non-gemcitabine containing arms and survival did not improve with the additional cytotoxic agent. Achieving a pCR was still prognostic for disease-free and overall survival, but not strikingly so. Three-year overall survival was 91% in those with a pCR, and 81% in those without pCR (P<0.0001). Since Neo-tAnGo began it has become evident that the prognostic value of pCR is greater for HER2 positive, high grade, and triple negative tumors (6); this finding was reflected in Neo-tAnGo. As expected, the addition of gemcitabine was associated with increased toxicity, particularly neutropenia, infection, fatigue and muscle or joint pain.

Several adjuvant and neoadjuvant trials have now demonstrated similar results to the Neo-tAnGo trial. NeoGem, our own small single-arm study of neoadjuvant EC followed by docetaxel and gemcitabine showed consistent results (7). The pCR rate was 20% for HER2 negative disease, but because trastuzumab was given for HER2 positive disease the pCR rate in this subgroup was 53%. The failure of gemcitabine to succeed in the neoadjuvant setting was an accurate reflection of the lack of a survival benefit seen in the companion adjuvant tAnGo trial which was presented 6 years ago (8).The tAnGo trial used the same EC and docetaxel chemotherapy backbone. If it had been known that the addition of gemcitabine in the neoadjuvant setting did not improve pCR, enthusiasm to proceed with a larger adjuvant trial may have been dampened. The recently presented German SUCCESS-A trial randomized 3,754 patients with high risk early breast cancer to adjuvant FEC-docetaxel either with or without gemcitabine (9), once again, gemcitabine did not add efficacy.

Interestingly Neo-tAnGo demonstrated a 5% improvement in pCR when the taxane containing component was given before the anthracycline (20% *vs*. 15%, P=0.03). This difference, despite reaching statistical significance, did not translate into a disease-free or overall survival advantage. These pCR results are similar to those seen in a large retrospective analysis of cases from the MD Anderson Cancer Center where neoadjuvant paclitaxel followed by FEC/FAC was compared with the reverse sequence (pCR 20.9% *vs*. 12.4%, P=0.003) (10). In this series, anthracycline-first scheduling was associated with a higher risk of relapse compared with taxane-first (HR 1.49, P=0.01). A taxane-first approach has also been evaluated in several prospective early breast cancer trials, the majority of which were phase II (11). Conflicting pCR results have been shown in neoadjuvant trials. Some, including Neo-tAnGo, demonstrated a small pCR difference favouring the taxane-first arm but in others, there was no difference. The main outcome difference in the adjuvant sequencing trials was the higher relative dose intensity of both the taxane and anthracycline components if the taxane was given first, but most trials were too small to show a difference in survival endpoints (10). Thus the difference in pCR shown in Neo-tAnGo is of interest but unlikely to be considered sufficiently clinically relevant and is unlikely to change practice.

The addition of other cytotoxic agents to standard anthracycline and taxane based regimens has been studied in the neoadjuvant and adjuvant settings. Capecitabine, another antimetabolite, also showed a survival benefit when combined with a taxane in the metastatic breast cancer setting. Like gemcitabine, this survival advantage has not translated into a significant benefit in earlier stage disease (12). NSABP B-40 is a randomised neoadjuvant trial that compared docetaxel alone versus in combination with either gemcitabine or capecitabine, followed by doxorubicin and cyclophosphamide (AC) (13). There was no difference in the pCR rate between the three arms. The adjuvant FinXX trial also showed no survival advantage with the addition of capecitabine to adjuvant taxane- and anthracycline-based chemotherapy (14). The lack of incremental benefit seen with the use of additional cytotoxic agents suggests that in an unselected population residual disease is chemoresistant, and requires alternative approaches.

There is renewed interest in incorporating platinum salts into the treatment of breast cancer, particularly in the basal subtype, and the neoadjuvant setting seems an ideal platform. The I-SPY 2 trial investigators showed an increased pCR rate (52% *vs*. 24%) in women with triple negative breast cancer arm treated with carboplatin, veliparib and paclitaxel, followed by AC, compared to the same protocol without carboplatin (15). The I-SPY 2 program represents a novel mechanism for selecting drugs

and combinations that are most likely to demonstrate a benefit in a phase III trial in one or more breast cancer subtypes. I-SPY 3 will then proceed with these 'graduates' for efficacy testing. This is supported by the GeparSixto trial in which the addition of neoadjuvant carboplatin to paclitaxel and non-pegylated liposomal doxorubicin increased pCR rate from 36.9% to 53.2% (P=0.005), at the expense of increased haematological toxicity (16).

Neo-tAnGo has not yet reported on molecular and genetic profiling, mutation analysis, and comparative genomic analysis of serial biopsy specimens that were taken during the trial. These translational endpoints are important to identify biomarkers that may predict response to novel therapeutic strategies, and have the potential to add significant value to the trial data. Neo-tAnGo defined pCR as 'absence of invasive breast cancer in the breast and axillary nodes', which falls short of the strict definition of 'no invasive or non-invasive residual in the breast or nodes' used by the German Breast Group (17). A central review of the pathology found that there was considerable variability in the reporting of surgical specimens after neoadjuvant therapy. The authors suggested that consensus guidelines should be implemented in order to improve the reliability of pCR as an endpoint (18). In addition to pCR, at least two pathological systems are used to quantify remaining breast cancer after neoadjuvant therapy: the residual cancer burden (RCB) (19) and the clinicopathologic score-estrogen grade (CPS-EG) (20). These scores are most relevant for hormone receptor positive disease, where the low rate of pCR does not provide sufficient risk stratification to determine which patients might benefit from additional therapy.

The linked design of tAnGo and Neo-tAnGo is important to help clarify the role of pCR as a surrogate endpoint for disease free survival and overall survival in the adjuvant setting (8). Ideally, longer follow up is needed in neoadjuvant trials to separate the predictive value of pCR from the prognostic value, but many of these trials do not follow patients beyond surgery. Whilst pCR is clearly prognostic, only one trial (NOAH) has demonstrated that a difference in pCR rate between trial arms correlates with survival outcomes (21). This correlation appears due to a large difference in HER2 positive patients treated with trastuzumab compared with a non-trastuzumab-containing neoadjuvant regimen. This is consistent with the adjuvant trastuzumab trials. Even with a doubling of pCR rate in the NSABP B-27 trial, using neoadjuvant AC with or without docetaxel (26% *vs.* 13%, P<0.0001), survival was no different (22). In the adjuvant setting, a meta-analysis has confirmed an overall survival when taxanes are added to adjuvant chemotherapy, but many of the individual studies were unable to demonstrate a difference (1).

In HER2 positive patients, the large adjuvant ALTTO trial recently showed that disease-free survival is no different with trastuzumab or a combination of trastuzumab and lapatinib with adjuvant chemotherapy (23). This is despite NeoALTTO, its neoadjuvant counterpart, showing a pCR rate of 51.3% with the combination of lapatinib and trastuzumab, compared with 29.5% using trastuzumab alone (P=0.0001) (24). ALTTO and NeoALTTO have added uncertainty to the role of neoadjuvant trials as a viable alternative to large phase III adjuvant trials, even in the HER2 positive subtype.

The value of pCR has been recognized by the United States Food and Drug Administration (USFDA) as an early trial endpoint for accelerated drug approval (25). The European Medicines Agency has recently echoed this recognition, with the caveats that there must be a well-characterised mechanism of action in an aggressive tumor type, with a major increase in pCR. The USFDA have indicated that this status is limited to breast cancer subtypes such as HER2 positive and triple negative, where an increase in pCR rate is 'reasonably likely' to correlate with clinically important endpoints of event-free and overall survival. Consequently, based on the NeoSphere trial, pertuzumab has USFDA approval for use in the neoadjuvant setting with trastuzumab and docetaxel, but is not yet approved for use after surgery (26). After the presentation of the ALTTO study, the ongoing value of pCR as a mechanism for accelerated approval of new agents is unclear for HER2 positive breast cancer. A correlation between pCR and survival has yet to be proven, or disproven, in patients with triple negative breast cancer.

The role of neoadjuvant systemic therapy continues to evolve, and is likely to remain an important clinical trial approach and in standard practice for some time to come. One future role is as a marker of poor prognosis to select for additional post-neoadjuvant therapy in those who have not achieved a pCR. The PENELOPE^{B} trial is testing this approach using endocrine therapy with or without palbociclib, a CDK 4/6 inhibitor, in patients with a high risk of relapse as indicated by their CPS-EG score (NCT01864746). Neoadjuvant trials evaluate the effect of novel therapeutic strategies on early breast cancer, which tends to exhibit fewer genomic alterations than metastatic breast cancer, which is where new drugs are traditionally first tested (27). Therefore, drugs which do not increase the rate of pCR in an appropriately selected population may

be removed from further testing without the need for large adjuvant trials with prolonged follow up.

The results of the Neo-tAnGo study, along with results of other related neoadjuvant and adjuvant studies, show that without a predictive biomarker, there is no role for the addition of gemcitabine to current chemotherapy regimens for early breast cancer (7,9,28,29). Paclitaxel-first scheduling is a reasonable option, but seems unlikely to have a significant impact on survival outcomes. Whilst the neoadjuvant approach remains important, this strategy has not yet been able to make the adjuvant trial redundant.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research* for the series "Breast Cancer". The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2014.06.11). The series "Breast Cancer" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Zdenkowski N, McCarthy N. Neoadjuvant chemotherapy: what does it take to tAnGo? Transl Cancer Res 2014;3(6):547-551. doi: 10.3978/j.issn.2218-676X.2014.06.11