Neoadjuvant trial design: time for a brave new world?

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In the NOAH clinical trial, trastuzumab treatment for locally advanced breast cancer, given prior to surgery, was associated with increased complete and overall response rate and improved event-free survival. The ability to identify this advantage suggests that the neoadjuvant setting might serve to inform the design of adjuvant trials and indicate appropriate off-study adjuvant therapy.

Locally advanced breast cancer (LABC) has not been consistently defined; however, it generally denotes inoperable tumours that are large, have extensive lymph node and/or skin or chest wall involvement as well as typically including the rare and aggressive inflammatory breast cancer subtype. LABC is associated with a worse prognosis than operable early-stage disease, but a better prognosis than metastatic disease.[1] Historically, patients with LABC were treated with modified radical mastectomy and radiotherapy alone, but with disappointing results. Thereafter, systemic therapy became an integral component of the LABC management strategy, largely as a consequence of the promising results reported with adjuvant systemic strategies in the early-stage breast cancer setting. Specifically, the administration of systemic neoadjuvant therapy before definitive surgery and radiotherapy induced tumour response and improved local control rates. The practice of delivering neoadjuvant chemotherapy, hormone therapy and/or biologic therapy affords a number of potential advantages, including downstaging of the primary tumour to allow for surgery and, in some cases, increasing the likelihood of a breast-conserving approach. From a research and therapeutic innovation perspective, because pathology is obtained at diagnosis and again at definitive surgery, neoadjuvant strategies permit a convenient and *in vivo* assessment of response to specific systemic therapies. Furthermore, because the event rates are higher in LABC than in early-stage disease, the follow-up time and the sample size required for LABC studies are typically modest in comparison. For these reasons, the neoadjuvant study model offers tremendous promise as an efficient drug development tool.

Up to 20% of breast cancers present with either amplification of the *HER2* gene or overexpression of its protein product, a transmembrane receptor tyrosine kinase, and are considered to be 'HER2-positive'. Trastuzumab is a humanised HER2-targeted monoclonal antibody that was developed through traditional translational drug development pathways. It was first studied *in vitro* and in animal models, then as monotherapy in phase I and II trials in patients with metastatic breast cancer,[2–4] then in combination with chemotherapy in randomised trials in the metastatic setting.[5] Ultimately it was tested in combination with proven adjuvant chemotherapy strategies,[6,7] where its use was associated with significant survival improvements.

The impact of treatment with trastuzumab in the LABC setting was recently evaluated in the NOAH study, an international, open-label, phase III trial.[8] The NOAH trial was originally designed to randomise women with HER2-positive, locally advanced or inflammatory breast cancer to neoadjuvant trastuzumab plus chemotherapy followed by adjuvant trastuzumab or to neoadjuvant chemother-

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apy alone. However, when the results from the first adjuvant trastuzumab studies were reported,[6,7] the trial design was altered so that 19 of the 118 women (16%) with HER2-positive breast cancer randomised to the chemotherapy-alone arm were offered a standard course of adjuvant trastuzumab (with analyses performed by intention-to-treat). This trial was unique in that it included an observational cohort of 99 women with HER2-normal LABC for comparison. After a median follow-up of 3.2 years there were significant improvements in the overall response rate (ORR), including a doubling of the total pathologic complete response (pCR) rate, and the event rate in the cohort receiving neoadjuvant trastuzumab and chemotherapy compared with those receiving chemotherapy alone. Specifically, for the 117 women who received chemotherapy with trastuzumab versus the 118 women allocated to receive chemotherapy alone, the pCR rate was 38% versus 19% (P=0.001), the ORR was 87% versus 74% (P=0.009), and the hazard ratio for event-free survival (EFS) was 0.59 (P=0.013) in favour of the trastuzumab arm. However, consistent with numerous other neoadjuvant reports, the improvements in pCR, ORR and EFS rates did not translate into overall survival benefits. Thus, the NOAH investigators appropriately concluded that, although the administration of neoadjuvant trastuzumab improved pCR rates, it is unknown whether the observed EFS benefits can be ascribed to the administration of neoadjuvant trastuzumab, adjuvant trastuzumab or the combination. Although to our knowledge there are no planned studies comparing EFS rates with neoadjuvant trastuzumab, adjuvant trastuzumab or the combination in LABC, such a study would not only inform LABC treatment recommendations but could also indirectly inform decisions in the early-stage setting where the optimal duration of trastuzumab treatment is not established.

It is now more than 20 years since the association between HER2 status and risk of relapse and death was published[9] so why did it take 20 years to get to this stage? While the results from the NOAH study were predictable (that is, trastuzumab confers benefits in HER2-positive LABC as it did in HER2-positive early-stage and metastatic breast cancer), it nonetheless leaves us with more questions than answers: Should trastuzumab be administered before surgery, after surgery or both? What is the optimal chemotherapy regimen for coadministration? Were there any biologic predictors of response or resistance to therapy? How will other promising HER2-targeted agents be incorporated into the LABC management strategy? Is there a more efficient paradigm for the timely evaluation of novel, promising therapeutic innovations? Would improved drug development paradigms have positively impacted the design and implementation of modern neoadjuvant studies of other HER2-targeted agents, including the tyrosine kinase inhibitor lapatinib (as in NeoALLTO, NSABP B41 and CALGB-40601) and the monoclonal antibody pertuzumab (as in NEOSPHERE)? How can we learn from our experiences so that novel HER2-targeted agents with promising activity in the metastatic setting (such as T-DM1 and HSP90 inhibitors) are evaluated efficiently?

Using traditional drug development strategies, it is difficult to fathom how we will begin to tackle the seemingly exponential growth of clinical questions. Possibly, the traditional model of drug development, whereby drugs are moved from the lab through a series of phase I to III studies in the metastatic setting before moving into the adjuvant setting and beyond, is too labour intensive, costly, inefficient and slow. Does the answer lie in the advantages and conveniences of the LABC model? If so, will we ever be brave enough to shed the traditional study paradigms, eliminate metastatic studies altogether (at least as a necessary step before neoadjuvant trials) and adopt a primary neoadjuvant study model? Imagine if the NOAH trial and the smaller neoadjuvant trastuzumab–chemotherapy study from MD Anderson Cancer Center[10] had been conducted at the onset of trastuzumab development, in all likelihood the adjuvant studies would have been conducted earlier, novel HER2-targeted therapy development may have been accelerated, and biologic-correlate studies might have advanced our understanding about HER2-positive disease faster. Certainly a paradigm shift is not without its challenges and drastic change will always be met with resistance, but it must be time to seriously consider such a brave new world!

Details of the references cited in this article can be accessed at www.cancerworld.org

Practice point

Since drug development in the metastatic breast cancer setting often relies on endpoints (such as response rate and progression-free survival) that are either loosely linked to overall survival or poorly predictive of ultimate activity in the adjuvant setting, novel approaches are needed. To the degree that in-breast response (such as pathologic complete response) can serve as a surrogate for progression-free survival and overall survival in the early-stage setting, neoadjuvant (preoperative) trials may facilitate faster and more efficient identification of promising new systemic therapy regimens.

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