Estimating risk of recurrence for early breast cancer – integrating clinical and genomic risk

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Prognostication of ER-positive HER2-negative breast cancer is critical for decision making on adjuvant therapy. Many cancer patients are cured by local therapy, with surgery and radiotherapy, and endocrine therapy alone. Confidently identifying patients who are cured so they can safely avoid chemotherapy is essential to minimise overtreatment. Several commercially available gene expression genomic classifiers are available to help identify cancers that are at such low risk of recurrence, that chemotherapy could not provide a meaningful improvement in outcome.

An unanswered question has been whether these genomic classifiers can give more information than just prognosis. In particular, can they confidently identify tumors that are insensitive to chemotherapy, such that even if the estimated risk of relapse based on clinicopathologic factors is sufficient to consider a course of chemotherapy, they can provide a classification that allows chemotherapy to be omitted from the patients' management?

Of the many genomic classifiers, the 21-gene Recurrence Score (RS; OncotypeDX), which has now been used in well over 500,000 patients[1], had retrospective data from the NSABP B20 randomised trial of tamoxifen±chemotherapy that suggested that cancers with an old intermediate score (RS 18-30 and 10-year risk of distant recurrence of 11-21%) might be relatively insensitive to chemotherapy[2]. There has been uncertainty about the interpretation of that finding: it was derived from a retrospective, secondary analysis of a patient population that contributed samples to the training of the RS and the intermediate risk group comprised only 134 patients of which just 45 were from the tamoxifen alone arm. In contrast to that small study, an EBCTCG overview analysis of about 100,000 patients, including about 10,000 randomised to anthracycline or no chemotherapy, found no difference in the proportional reductions in risk of recurrence between any subgroups including those defined by histopathologic grade, ER versus negativity or level of ER positivity[3]. The EBCTCG findings surprised many since they are in stark contrast with the strong correlations these markers show with response to chemotherapy in the neoadjuvant setting[4]. Oncologists regularly seeing patients responding or not to

neoadjuvant chemotherapy according to these biologic factors may be receptive to the concept of molecular predictors of long-term benefit from adjuvant chemotherapy, while evidence for such differences is slim at best.

The observation of possible prediction of chemotherapy sensitivity in the B20 study was sufficiently important for the TAILORx study to be designed to test whether chemotherapy is beneficial for women with a new intermediate, or mid-range RS of 11 to 25 and who met National Comprehensive Cancer Network guidelines for the recommendation or consideration of adjuvant chemotherapy[5]. Yet for a variety of reasons TAILORx has not answered the question definitively. This raises a number of critical issues of more global importance to be considered for estimating risk in clinical practice and future clinical trial design.

Many recent phase III adjuvant studies have reported lower event rates than predicted by historically based estimates, and have either extended their follow-up time or increased the sample size; either way the population tested was of lower risk than expected[6-9]. It might have been anticipated that this would be minimal in TAILORx where modern molecularly based estimates of risk were a key entry criterion. Yet TAILORx presents one of the starkest examples of recent adjuvant trials. The study was planned in anticipation of 87% 5-year invasive disease-free survival (iDFS; primary end-point) in the RS 11-25 group randomised to endocrine therapy only. Yet the 5-year iDFS was 92.8% and 5-year distant metastasis-free survival was 98%. For the primary end-point, 59.5% of events were not related to the original cancer. The very substantial difference between anticipated events rates, and actual, may have reflected the very low risk patient population recruited: median 1.5cm tumor size, and 86% low-intermediate grade.

The low breast cancer event rate for the study challenges the interpretation of its results. With 98% of patients in the endocrine only arm being free from distant recurrence at 5 years, the study has not been able to address whether intermediate risk cancers are chemotherapy sensitive, the original objective of

the study. Instead patients in the randomized population recruited had such a good prognosis, chemotherapy was irrelevant. This is a very positive outcome for patients, with node-negative disease and tumors similar to those recruited into the randomised part of the study but it poses challenges to the generalizability of the finding to patients with higher stages of disease.

Most importantly, it is clear that integration of clinical parameters and molecular scores improves the accuracy of prognostic estimates. Indeed the much lower than expected relapse rate could potentially have been anticipated in the randomised population to TAILORx, if clinical factors had been integrated into the estimate of risk. An earlier study found that only about 5% of the variability in risk estimates made by Adjuvant Online was explained by estimates by OncotypeDX[10]. This prompted a study that combined data from NSABP-14 and TransATAC on patients treated with only endocrine therapy to create the RS-pathology-clinical (RSPC)[11]. The RSPC included RS, age, tumor size, grade and type of hormonal treatment and provided a risk estimate that provided significantly improved prognostic value over RS alone. Strikingly, only 28% of the 385 patients that had an intermediate RS (18-30) were characterised as intermediate risk by RSPC, while 55% of that group were downstaged by RSPC to low risk. The importance of integrating certain clinical factors with genomic prognostic scores is recognised by other genomic predictors such as Endopredict and ProSigna, in which tumor size is automatically integrated with molecular risk. It is also important to note that the type of endocrine therapy is important, and yet test results do not factor this in; the relative risk of breast cancer mortality on an aromatase inhibitor is approximately 15% lower than with tamoxifen[12]. Notably, while the MINDACT trial did not fully integrate clinical and molecular scores it created four categories according to high/low risk for both clinical and molecular features[13].

The data from TAILORx suggest that the traditional definition of iDFS is no longer the best end-point for clinical trials. Including occurrence of new cancers of any type in the definition, which are very unlikely to be affected by the randomisation, resulted in 35% of the events in the primary endpoint, greater

than the number of distant recurrences. New definitions of iDFS without second cancers may become a standard for future studies.

TAILORx also demonstrates the limitation of non-inferiority study designs for low risk populations. Although TAILORx technically demonstrated non-inferiority of endocrine therapy versus chemotherapy and endocrine therapy for mid-range RS (five year iDFS hazard ratio 1.08; 95% confidence interval, 0.94 to 1.24; P = 0.26), this may have been the result of the low breast cancer event rate, and high number of non-breast cancer events in the primary endpoint. This has important implications for applying the result to stage II (and stage III) breast cancers, where the benefit from chemotherapy for these cancers of intermediate score has not yet been answered. The ongoing RxPONDER study will address this for node-positive disease (NCT01272037).

There are implications for future studies in low risk patient populations. A cohort study may be able to change clinical practice, if a well-characterised cohort can be derived that will show sufficiently good outcome to negate benefit from additional treatment. This was demonstrated by the extremely low event rates of the low risk (RS<11) TAILORx population[14]. Similarly, the 98.7% 3-year iDFS of a cohort of patients with small HER2+ tumours treated with paclitaxel and trastuzumab excludes meaningful benefit from adding more toxic chemotherapeutics[15]. Such cohort studies will likely report many years earlier than non-inferiority studies. Additionally, if the cancer event-rate in a non-inferiority trial is substantially lower than anticipated, the study may not address the original objective. It is therefore highly important to ensure the risk profile of patients recruited will give the anticipated event rate, with the data monitoring committee primed to monitor this.

A particularly striking subgroup analysis in TAILORx identified a large benefit for chemotherapy in young patients with intermediate risk scores above 15. The potential pitfalls of unplanned retrospective subgroup analysis in clinical trials are well documented, most eloquently first demonstrated in the ISIS-2 trial, where astrological star sign associated with benefit from aspirin after a

myocardial infarction[16]. Examples are frequently observed in cancer trials; for example patients with HER2-positive non-visceral disease derived no benefit from pertuzumab in overall survival in the CLEOPATRA trial[17]. Such chance observations are frequent in subgroup analyses.

Of note the young patient subgroup analysis in TAILORx was retrospective, not pre-planned, and presents one subgroup (age) further subdivided by ranges of RS (11-15, 16-20 and 21-25). The analysis suggested that premenopausal patients with an RS of 16 or greater may in contrast to the rest of the randomised population derive benefit from chemotherapy[5]. Yet the number of distant recurrences in the <=50 RS subgroups is very small, 16, 27 and 26 events respectively. We suggest that this should be considered a hypothesis-generating result. The Oxford EBCTCG meta-analyses in unselected patients, with many thousands of events, suggests moderately worse prognosis for young women, and modestly greater benefit from chemotherapy, but no major differences compared to older women[18]. Chemotherapy induced menopause in the <50 age group may also have contributed to the observed effect, as the study pre-dated the SOFT and TEXT studies demonstrating the benefit of ovarian suppression in premenopausal women[8,9]..

What does a practicing clinician do with the results of the TAILORx study? We expect this to be the subject of future guidelines, and we give our view as an interim measure.

Firstly, risk estimates from molecular factors should be considered together with standard clinico-pathologic factors (tumor size, grade, nodes, age, type of endocrine therapy) and not in isolation. Without integration, a clinician may decide to offer chemotherapy to a patient with a 10mm ER positive cancer with a RS of 27 (high risk score by TAILORx), and not offer chemotherapy for a 40mm ER positive cancer with a RS of 23 (intermediate risk score by TAILORx). Yet the second patient is at substantially greater risk of relapse, and likely to derive substantially more benefit from chemotherapy. The tools to integrate clinical

features with Oncotype are readily available[18] and clinicians using Oncotype may wish to consider using them routinely.

Secondly, to derive chemotherapy benefit estimates from combined molecular and clinical risk the following should be considered. Stage I and II, lymph node-negative ER-positive cancers </=3cm with a low risk score have such a low event rate to not require chemotherapy[5,14] Similarly, TAILORx demonstrates that stage I cancers with an intermediate risk have such a low risk of recurrence they could not benefit from chemotherapy. Yet, the chemotherapy sensitivity of stage II/III cancers with intermediate risk has not been answered as yet. Oxford overview data[3] suggests that third generation adjuvant chemotherapy reduced the risk of mortality by approximately 35% allowing estimates of chemotherapy benefit from RSPC.

Thirdly, for cancers with intermediate scores and higher clinical risk, chemotherapy may still be appropriate as discussed above. The TAILORx study recruited very few patients with tumors greater than 3cm, and no patients with node positive tumors; the RxPONDER study will address node positive patients.

Lastly, as noted above it is well-documented that women of young age, have a higher risk of relapse and overall a modestly greater benefit from chemotherapy[19]. Beyond this, there is no strong data to suggest that cancers of intermediate risk 21-gene RS have fundamentally different sensitivity to chemotherapy in young versus older women. Age should therefore be factored into decisions about chemotherapy, but should not be a major driver in decision-making. Premenopausal patients with intermediate risk should likely be considered for ovarian suppression[8,9].

In summary and conclusion, the TAILORx study has been one of the most ambitious and important biomarker studies conducted in oncology. The study re-emphasises the ability to avoid chemotherapy in most stage I ER-positive HER2-negative cancers, and aids in our decision making in stage II cancers with tumour sizes up to 3cm. Most importantly the study stresses the critical

importance of integrating molecular and clinical risk in routine practice, eg with RSPC. This general issue should be factored into routine clinical care; clinical trial design may then encompass better powering and meet the trial's objectives within targeted recruitment and contemporary clinical practise.

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