Adjuvant chemotherapy—yes or no? Prognostic markers in early breast cancer

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The question of whether to offer adjuvant chemotherapy to patients with early-stage breast cancer continues to challenge clinicians on a daily basis. Many patients with node-negative or low-risk breast cancer could be spared the trauma of receiving chemotherapy, but more reliable prognostic markers are still needed to aid our therapy decision making. Gene expression profiling is a welcome product of the ‘omic’ era and several multi-gene expression panels (‘signatures’) have now been developed that show promise in predicting which breast cancer patients are likely to develop metastatic disease if adjuvant chemotherapy is not administered. The value of gene expression profiling as a prognostic tool in clinical practice is currently being appraised more fully in two large, prospective, randomised studies—TAILORx and MINDACT. These studies should provide level I evidence of the prognostic power of gene expression profiling and will hopefully allow us to one day quantify risk of progression in the individual patient and tailor treatment accordingly. Genetic profiling of circulating tumour cells and micrometastases should further enhance our understanding of breast cancer biology and allow us to personalise therapy based on functional maps of critical tumour pathways. Close collaboration between clinicians and scientists will be essential to achieve this goal.

Key words: breast cancer, gene expression profiling, adjuvant chemotherapy, prognosis

introduction

Adjuvant chemotherapy significantly improves disease-free and overall survival from breast cancer in both node-negative and node-positive patients. In node-negative patients, however, who generally have a better prognosis, the actual benefits gained from chemotherapy may be modest—particularly in endocrine-responsive disease—whereas the potential for toxicity remains [1, 2]. The large National Surgical Adjuvant Breast and Bowel Project (NSABP) trials B-14 and B-20 demonstrated that women who have node-negative, ER-positive breast cancer and who are treated with tamoxifen alone after surgery have an average 10-year recurrence rate of only ~15% [2], suggesting that 85% of women with this type of breast cancer would be exposed unnecessarily to the toxicity of chemotherapy if it were offered to all.

Despite a growing body of evidence that adjuvant chemotherapy may be unnecessary in a significant proportion of patients with early-stage breast cancer, a recent survey of experts reveals how uncomfortable we still are not offering chemotherapy to these patients. In this survey, which was conducted by our own unit, 40 breast cancer experts from around the world were asked how they would treat a 61-year-old, fit, post-menopausal, node-negative woman with primary grade 2 invasive ductal carcinoma that was 0.9 cm, HER-2 negative and endocrine unresponsive. Surprisingly, less than half (48%) reported that they would not treat such a patient; 25% said they would offer CMF, 13% would offer AC, 4% would offer tamoxifen and 8% would offer other treatments (e.g. FAe).

An array of international and national breast cancer treatment guidelines provide recommendations for the use of adjuvant chemotherapy in early-stage breast cancer. All reflect the difficulties encountered by clinicians on a daily basis in choosing the right treatment for the right patient at the right time, and all highlight the need for better ways of deciding who can be spared chemotherapy and predicting which treatment will work best for each patient [3, 4]. Currently, internationally-recognised guidelines such as those from the National Comprehensive Cancer Network [5] and the St Gallen consensus group [6] base their recommendations for the use of adjuvant therapy in early-stage breast cancer primarily on the patient’s endocrine responsiveness and the presence or absence of the HER-2 gene. However, endocrine responsiveness is uncertain in the presence of a high tumour grade and a high rate of proliferation.

Other traditional prognostic factors such as the presence of cancer in the axillary lymph nodes and tumour size (which reflects tumour bulk rather than tumour biology) are now considered to be of secondary importance when deciding which patients with early-stage breast cancer should receive adjuvant chemotherapy, according to the St Gallen guidelines.
improving prognostic indicators in early-stage breast cancer

The decision to use endocrine therapy or chemotherapy or both in early-stage breast cancer must always be based on balancing the expected absolute risk reduction with the patient’s willingness to experience toxicity in order to achieve that goal. Most clinical guidelines assign risk categories to patients with early-stage breast cancer, and these categories subsequently define the recommendations for adjuvant treatment options.

The St Gallen guidelines, for example, suggest that patients with early-stage breast cancer at low risk (and who could therefore possibly be spared adjuvant chemotherapy) are node-negative patients with all the following features: pathological tumour size ≤2 cm, grade 1, absence of peritumoural vascular invasion, HER-2/neu gene neither overexpressed nor amplified and age ≥35 years [6]. Node-negative patients with at least one of the following features are considered to be intermediate risk and therefore possible candidates for adjuvant chemotherapy: pathological tumour size >2 cm, grade 2–3, presence of peritumoural vascular invasion, HER-2/neu gene overexpressed or amplified, age <35 years [6].

Many oncologists also use the pioneering computer programme Adjuvant! on-line (http://www.adjuvantanline.com) to make joint decisions with their patients on the potential benefit of adjuvant therapy in each individual set of circumstances. This system was developed by Ravdin and colleagues in San Antonio, Texas [7], and is frequently used in the clinical setting to project the outcomes of different endocrine or chemotherapy options based on patient information and on tumour staging and characteristics such as tumour size, number of positive axillary nodes, and oestrogen receptor status. Outcomes for overall survival and disease-free survival and the improvement seen in clinical trials of adjuvant therapy are well modeled by Adjuvant! on-line, although validation for all types of patient with all treatment options is currently not possible.

Gene-expression profiling—which is a welcome product of the ‘omic’ era in which we all now work—looks set to further enhance our ability to predict risk and treatment responsiveness in early-stage breast cancer. Gene expression analysis evaluates which genes are actively transcribed into messenger RNA prior to translation into their product proteins in a tissue sample, and differences in the level of expression of specific genes can be correlated with cancer types and/or clinical outcomes.

Current techniques for gene expression analysis include cDNA microarrays, oligonucleotide arrays and quantitative real-time reverse transcriptase polymerase chain reaction (RT–PCR). Broad-scope genomic cDNA microarrays can be used to search for specific expression patterns with strong associations with cancer types or clinical outcomes (i.e. the likelihood of recurrences or metastases) using tumour tissue samples from clinically representative populations. An alternative approach is to select a large number of candidate genes already known to be associated with a key cancer pathway, and from these identify those with the strongest prognostic value. In both cases, the goal is to construct a smaller panel using the markers with the strongest associations with the characteristics of interest, and to validate the panel in a clinical setting.

Several research groups have constructed different multi-gene expression panels (‘signatures’) that are now in various stages of clinical testing. Paik et al [8] have developed a 21-gene assay (Oncootype DX) that was validated on banked tumour tissue from patients in the NSABP B-14 trial and used to develop a recurrence score (RS) algorithm for patients treated with tamoxifen in this study. Using this panel, the rates for distant recurrence in tamoxifen-treated patients with node-negative, oestrogen receptor-positive breast cancer at 10 years were reported to be 6.8% for those with a low RS (<18), 14.3% for those with an intermediate RS (18–30) and 30.5% for those with a high RS (≥25) [8]. In a multivariate Cox model, the recurrence score had significant predictive power that was found to be independent of the patient’s age or tumour size.

Van’t Veer et al [9] have used DNA microarray analysis to study a narrowly defined sub-set of breast cancer patients (those aged <55 years who were diagnosed with tumours smaller than 5 cm, had no nodal involvement or axillary metastases and were treated only with local–regional therapies) and found that the expression of 231 genes was statistically significantly associated with disease outcome, as defined by the presence of distant metastasis within 5 years. This group of genes was subsequently reduced to a core set of 70 genes that together constituted a signature (now known as the ‘Amsterdam’ signature) of substantial prognostic value. The 70-gene signature was subsequently applied to a larger set of 295 breast cancer patients from the same institution [10], and the results confirmed that the signature could clearly distinguish patients according to their 10-year survival outcome.

More recently, Wang et al [11] have published the results of a microarray study in which they identified a 76-gene signature that was highly informative in identifying patients with node-negative breast cancer who developed distant metastases within 5 years, even when corrected for traditional prognostic factors in a multivariate analysis. This 76-gene signature (sometimes referred to as the ‘Rotterdam’ signature) has now been validated in a further study of patients with node-negative breast cancer [12] which confirmed that the signature was strongly prognostic in sub-groups of patients with oestrogen receptors, in pre- and post-menopausal women, and in patients with tumours ≤2 cm.

Although these and many other smaller studies have generated promising data to suggest a future role for gene expression profiling in predicting which patients with early-stage breast cancer are likely to develop metastatic disease without adjuvant chemotherapy, small sample sizes, varying assay methods and retrospective methodologies have so far limited the application of this technology in therapeutic decision making. In an effort to systematically review the test performance of various gene expression signatures in women with early-stage breast cancer, Lyman and Kuderer [13] have recently undertaken a meta-analysis of published studies assessing the relationship between gene expression signatures and recurrence-free survival. In their analysis, 17 cohorts of patients with primary breast cancer (n = 2908) were reviewed;
7 cohorts were evaluated using cross-validation techniques and 10 were studied in independent cohorts. Overall, 52.6% of patients were classified as high risk based on a gene expression assay, and 20.5% experienced distant breast cancer recurrence during the period of observation. The reported recurrence rates were 31.2% among gene expression profile patients at high risk and 8.5% among patients at low risk. Median follow-up on patients in these studies ranged from 2 to 14 years.

Our group has gone one step further and undertaken a meta-analysis (as yet unpublished) of publicly available gene expression data from breast cancer studies involving a total of 2865 patients. We found a high degree of concordance between different gene expression-based predictors of disease progression. A particularly strong and independent association was found between the proliferation genes contained in these signatures and prognosis. Multivariate analysis in patients in whom data on all variables were available demonstrated that a high-risk gene signature was the most effective of all prognostic indicators. Interestingly, nodal status and tumour size were the two standard clinical predictors that remained significant in the model.

**impact of gene expression profiling on patient care**

As promising as gene signatures appear to be in predicting which patients with early breast cancer should receive adjuvant chemotherapy and which could be spared treatment, it still needs to be proven that they provide additional useful information to the clinical and pathological risk criteria that are currently used, and several research groups are working hard towards that goal. Buyse et al [14], on behalf of the European Union (EU)-supported TRANSBIG consortium, have recently compared the ability of the 70-gene signature to predict 5-year distant metastasis-free survival and 10-year survival with risk estimates generated using the 2003 St Gallen clinical and pathological criteria [15] and the Adjuvant! software. The study was conducted at five European centres and included 326 patients who had been diagnosed with breast cancer between 1980 and 1998 and had a median follow up of 13.6 years. Patients were eligible to participate if they were younger than 61 years and had node-negative, T1–T2 (≤5 cm) breast cancer at diagnosis, and had not received adjuvant systemic therapy.

The study confirmed that the 70-gene signature was a strong prognostic factor for time to distant metastases and overall survival in untreated patients with node-negative breast cancer, with unadjusted hazard ratios of 2.32 (95% CI: 1.35–4.00) and 2.79 (95% CI: 1.60–4.87), respectively. The gene signature remained a statistically significant prognostic indicator of time to distant metastases and survival even after adjusting for clinical and pathological factors known to have prognostic value in this disease. The 70-gene signature, the Adjuvant! software, and the St Gallen criteria all showed high sensitivity for metastases within 5 years (0.90, 0.87 and 0.96, respectively) and for death within 10 years (0.84, 0.82 and 0.95, respectively) (Figure 1a), suggesting that all three tools carry a minimal risk of falsely classifying a patient as low risk when they will subsequently die from breast cancer. However, the 70-gene signature had higher specificity for metastases within five years (0.42, 0.29 and 0.10, respectively) and for death within 10 years (0.42, 0.29 and 0.10, respectively) (Figure 1b) than the Adjuvant! software and the St Gallen criteria, suggesting that gene expression profiling may be the best tool to reduce the risk of falsely classifying a patient as high risk and exposing them unnecessarily to adjuvant chemotherapy. That said, there is still room for improvement in identifying patients with a good prognosis.

The value of gene expression profiling as a prognostic tool in clinical practice is currently being evaluated more fully in two large, prospective, randomised studies—TAILORx and MINDACT (Figure 2). Both studies, conducted in women with node-negative breast cancer, aim to provide level 1 evidence that the use of the gene predictor does not compromise survival, and spares a proportion of women the side-effects and costs of adjuvant therapy.

The Trial Assigning IndividuAlized Options for Treatment (Rx) (TAILORx), which is sponsored by the National Cancer Institute (NCI) and co-ordinated by the Eastern Cooperative Oncology Group (ECOG), aims to enroll over 10 000 women at 900 sites in the USA and Canada [16]. Women recently diagnosed with oestrogen receptor- and/or progesterone receptor-positive, HER-2/neu-negative breast cancer and who have recently undergone surgery will be eligible for inclusion.
Patients will be assigned to one of three groups based on their risk of distant recurrence determined by the Oncotype Dx 21-gene assay: a low-risk group (RS <11), a medium-risk group (RS 11–25) and a high-risk group (RS >25). Patients in the low-risk group will receive standard hormonal therapy (e.g., tamoxifen or aromatase inhibitor) at the discretion of the treating physician for 5–10 years; patients in the medium-risk group will be stratified according to tumour size, menopausal status, planned chemotherapy and planned radiotherapy and then randomised to receive either hormone therapy alone or combination chemotherapy and hormonal therapy; patients in the high-risk group will receive combination chemotherapy followed by hormone therapy. The primary aims of the study are to compare the outcomes of patients in the medium-risk group treated with adjuvant combination chemotherapy and hormone therapy versus those treated with adjuvant hormone therapy alone. Importantly, however, the study will also determine if adjuvant hormonal therapy alone is sufficient treatment for patients with a low-risk gene expression score. Follow-up will be for up to 20 years.

The Microarray In Node negative Disease may Avoid Chemotherapy Trial (MINDACT), which will be conducted by the Breast International Group and co-ordinated by the European Organisation for the Research and Treatment of Cancer—Breast Cancer Group, will enroll 6000 node-negative women aged 18–70 years with early-stage breast cancer irrespective of hormone receptor and HER-2 status [14, 17]. Assessment of risk will be made using both the 70-gene signature and the Adjuvant! software. Those patients considered to be at high risk on both tools will be treated with chemotherapy (plus hormone therapy where appropriate); those at low risk on both tools will receive hormone therapy where appropriate. Patients in whom the risk scores generated by each tool are discordant will be randomly assigned to have their treatment decision (i.e., adjuvant chemotherapy or not) made dependent on either the gene signature or Adjuvant! software. The predicted outcome for this part of the study is that the low-risk group (as defined by the gene signature) will have an excellent distant metastases-free survival at 5 years without adjuvant chemotherapy, thus sparing a substantial proportion of women who previously would have received adjuvant chemotherapy (because they were deemed to be at high risk of relapse by Adjuvant! software) unnecessary toxicity [14]. This trial will provide level 1 evidence of the clinical relevance of the 70-gene signature and, because biological material will be collected from all study participants, will offer great potential for the identification and validation of additional gene signatures in the future.

gene signatures beyond the primary tumour

Gene expression profiling of the primary tumour undoubtedly offers the hope that, one day, we will be able to tell a significant number of our early-stage breast cancer patients—with confidence—that they do not need adjuvant chemotherapy. Research into the prognostic potential of different tumour gene signatures is relatively advanced, and may soon enhance our levels of confidence; however, it seems likely that the primary tumour code may not tell the entire story, and that we should also be searching for other prognostic messages hidden within circulating tumour cells or end-organs such as the bone marrow [18]. Micrometastases in the bone marrow of early-stage breast cancer patients are known to be correlated with other prognostic indicators of early relapse such as tumour size and grade, lymph–vascular invasion and local lymph node infiltration [19–21], as well as with overall survival [20, 22]. More recent studies have confirmed that the presence of micrometastatic breast cancer cells in the bone marrow could be a valuable indicator of a poor prognosis [23–26], although quality issues relating to the technologies used to detect tumour cells in these and similar studies have been raised [27]. Gene
expression profiling of circulating tumour cells, which overcomes many of the technical limitations of immunohistochemistry and can be performed on peripheral blood, has the potential to provide additional prognostic information in early-stage breast cancer, and preliminary studies assessing the prognostic value of circulating cytokeratin-19-positive cells seem promising [28, 29].

Our own group has recently undertaken an independent validation of the 76-gene ‘Rotterdam’ signature to predict distant metastases in lymph node-negative breast cancer patients and reported a strong time dependency of the signature [30]. Gene expression profiling of frozen samples from 198 untreated patients was performed and a survival analysis was undertaken with the genomic risk, adjusted for the clinical risk, as defined by Adjuvant! on-line. Patients with a poor prognostic gene profile were found to be up to 13 times more likely to relapse at distant sites than patients with a good prognostic gene profile, although the predictive power of the signature began to weaken markedly after 5 years, suggesting that factors determining early relapse may differ from those determining late relapse.

prognostic markers and hopes for the future

Combining the gene expression profiles of primary tumour signatures with those of circulating tumour cells and bone marrow micrometastases would likely give us a far better insight into breast cancer biology, allowing us to accurately predict outcomes well into the future and individualise adjuvant therapy accordingly. Our hope is that, by 2012, with the help of molecular oncologists and other basic scientists, we will be able to personalise adjunctive chemotherapy based on functional maps of key pathways within malignant tumours and move away from our less than satisfactory ‘one shoe fits all’ approach to early breast cancer treatment. In order to do so, we need to accept that future adjunctive trials will be more complex and more costly and will require close international collaboration and dialogue between clinicians and scientists. There seems little doubt that the future of breast cancer treatment will be shaped by scientists and that interdisciplinary co-operation will be the key to success.

disclosures

The authors have no conflicts of interest to declare.

references

