Potential Utility of an Expression Array Signature for Predicting Anthracycline Responsiveness or Resistance

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Breast cancers, like other malignancies, are heterogeneous in terms of their molecular genetic alterations, gene expression patterns, clinical outcomes, and response to various therapies. This complexity has been characterized with various methods including expression array analyses, which have been used to define breast cancer subtypes according to identified predominant patterns of gene expression (Table 1). These subclasses are correlated with clinical outcomes and, therefore, represent prognostic markers (Table 1). However, therapeutic decision making is now being primarily based on the status of individual predictive markers such as estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2). These markers are used to select patients for treatment with specific therapies including antiestrogens, HER2-targeted agents, and/or chemotherapeutics. RNA array analyses permit characterization of expression of individual markers on a gene-by-gene basis and allow for analyses of combinations of gene expression across the entire genome. This has allowed for correlation of various expression patterns with responsiveness to any of a number of administered therapies. Although it had been expected that such detailed analyses across the entire range of known genes would reveal clear patterns of gene expression closely associated with specific responses to particular treatments, this goal has remained largely elusive.

In *Journal of Clinical Oncology*, Desmedt et al¹¹ report a microarray expression study designed to address the need for a gene expression profile associated with patient response to anthracyclines. This anthracycline-based score (A-score) uses three separate expression signatures: a *TOP2A* gene expression module and two previously

published expression modules related to tumor microenvironment. The *TOP2A* gene expression module is based on *TOP2A* plus a series of genes near *TOP2A* on chromosome 17q, whereas the other two modules comprise a tumor invasion/stroma expression module with *PLAU/uPA* as the prototype gene¹² and an immune response expression module with *STAT1* as the prototype gene.¹² These expression profiles are combined to derive a numerical score that is then used to predict incremental sensitivity to anthracycline-containing chemotherapy. The investigators evaluated this A-score in patients with ER-negative breast cancer treated in two neoadjuvant trials in which either anthracycline-based or a combination of taxane and anthracycline treatments were administered.

The study population consisted of patients from the TOP (Trial of Principle) study (n = 139 patients) who underwent pretreatment biopsies followed by neoadjuvant epirubicin monotherapy followed by surgical resection and assessment for pathologic complete response (pathCR). Participants in two validation cohorts, both restricted to ER-negative patients, were used to confirm the initial findings. One of the validation cohorts was a subgroup of patients from the EORTC (European Organisation for Research and Treatment of Cancer) 10994/BIG (Breast International Group) 00-01 trial. Gene expression data were available for 118 ER-negative tumors: 63 (26 pathCRs) in the anthracycline-based arm and 55 (23 pathCRs) in the combined taxane/anthracycline arm. The other validation cohort included all 86 ER-negative patients from the MDACC (MD Anderson Cancer Center) 2003-0321 trial, consisting of 45 patients (15 pathCRs) from a combined taxane/anthracycline arm and 41 patients (five pathCRs)

Table 1. Summary of Expression Array Signatures in Breast Cancers

Expression Array Signature	No. of Genes	No. of Patients	Indication	Clinical Utility	Treatment Selection
Intrinsic Subtype ^{1,2}	456	84	Invasive	Prognosis	None
MammaPrint ^{3,4}	70	295	Node negative	Prognosis	None
<i>HOXB13/IL17BR</i> ^{5,6}	2	60	ER positive	Prognosis, tamoxifen resistance ⁷	Additional therapy
Wound Response ⁸	95	295	Invasive	Prognosis	None
Invasiveness ⁹	186	581	Invasive	Prognosis	None
Stromal ¹⁰	50	63	ER negative	Treatment resistance	Anthracyclines
A-score ¹¹	186	320	ER negative	Anthracycline resistance	Anthracyclines

Abbreviations: A-score, anthracycline-based score; ER, estrogen receptor.

from an anthracycline-based arm. Gene expression data were available for all of these patients. None of the populations in the two validation studies contained a nonanthracycline arm that could be compared with these anthracycline-based treatment arms.

The authors also measured *HER2* and *TOP2A* gene amplification status using fluorescence in situ hybridization (FISH), *TOP2A* (topoisomerase II alpha) mRNA using reverse transcriptase–polymerase chain reaction, and *TOP2A* protein using immunohistochemistry. These results were also evaluated for association with pathCR at surgery and revealed that *HER2* amplification trended toward a significant correlation with pathCR (odds ratio, 3.02; $P = .052$), and *TOP2A* amplification was strongly and significantly correlated with pathCR (odds ratio, 14.5; $P < .001$).¹¹ In contrast, neither *TOP2A* mRNA level nor *TOP2A* protein staining correlated with pathCR ($P = .59$ and $P = .33$, respectively). As observed in a number of other studies, Desmedt et al¹¹ report that all patient cases with *TOP2A* gene amplification and most with *TOP2A* gene deletions (13 of 15) are found in the *HER2*-positive subgroup of human breast cancers and, accordingly, also contain *HER2* amplification.^{13–17} The fact that *TOP2A* gene amplification correlates with pathCR but *TOP2A* expression does not is not surprising. *TOP2A* gene amplification represents a structural mutation characteristically associated with constitutive gene expression, whereas increased *TOP2A* mRNA and protein expression in *TOP2A* nonamplified cells vary considerably over time, because normal (nonamplified) expression of this gene is tightly regulated by entry into the cell cycle.^{18–20} Consequently, increases in *TOP2A* expression can result from gene amplification or occur as a result of some proportion of the malignant cell population going through division. In cancers lacking *TOP2A* gene amplification, it is possible that dividing tumor cells may be more affected by anthracyclines, whereas noncycling cells may be less sensitive to anthracycline. In *TOP2A* amplified patient cases, tumors cells would have constitutively high expression. This is important to note because Desmedt et al do report a significant association between *TOP2A* amplification and anthracycline response as measured by pathCR; however, they chose not to use *TOP2A* gene status alone as the predictive marker. The stated reason for this is the high interlaboratory discordance rate observed for *TOP2A* determined by FISH in a meta-analysis performed by Di Leo et al.²¹ This observation contrasts with and differs markedly from reports that interlaboratory variability is low for FISH assays in general,²² FISH assays for *HER2*,²³ and, more to the point, FISH assays for *TOP2A*.¹⁷ Desmedt et al also state that isolated markers might not be sufficient to predict response or resistance to treatment because “a comprehensive view of the disease is needed.”^{11(p1580)} Although it is true that single gene markers may not reflect the full molecular, biologic, or clinical heterogeneity within subgroups, this perspective contrasts with the current practice of using various single genes as useful predictive markers. *HER2* and ER/progesterone receptor status are used to select patients for targeted therapies, such as trastuzumab and lapatinib or antiestrogen therapies, such as tamoxifen, aromatase inhibitors, and ER-downregulating agents. Moreover, a particular strength of these single predictive markers has been that their absence carries the ability to identify patients not likely to benefit significantly from these targeted therapies (ie, negative predictive value).

Given that there are multiple mechanisms responsible for variation in *TOP2A* expression levels (including some that are normal), it is not surprising that Desmedt et al¹¹ demonstrate that *TOP2A* expression as determined by reverse transcriptase–polymerase chain

reaction or immunohistochemistry does not correlate with responsiveness to anthracyclines. Similarly, expression array measurements of *TOP2A* mRNA alone would also be expected to lack correlation with anthracycline response. Although not stated in their report, it seems probable that this lack of *TOP2A* expression levels correlating with pathCR may be an important rationale for evaluating 23 genes from the *TOP2A* region on chromosome 17 as a surrogate for *TOP2A* amplification by FISH.¹¹ When *TOP2A* is amplified, there is a high probability that several genes adjacent to *TOP2A* will be coamplified as part of the same amplification event. Consequently, expression of the genes in the authors' *TOP2A* signature serves as a surrogate for identifying patient cases with *TOP2A* gene amplification, circumventing the need for a FISH method, which the authors state has significant interlaboratory discordance. Desmedt et al go on to state “that a weighted average of the expression values of *TOP2A* and several additional genes that are coamplified with *TOP2A*, but are not part of the smallest region of amplification of *HER2*, would give more quantitative and reproducible results than those provided by FISH.”^{11(p1582)} However, they fail to provide any data regarding the frequency with which the 23 genes are coamplified with *TOP2A* or how their expression as part of the *TOP2A* signature correlates with *TOP2A* gene amplification. To address this, we evaluated the issue of frequency with which the other 22 genes are coamplified and overexpressed with both *HER2* and *TOP2A* using single nucleotide polymorphism and expression microarray data from 51 known, genomically characterized human breast cancer cell lines (Figs 1A, 1B).²⁴ The *TOP2A* signature of Desmedt et al is an averaged sum of 23 genes on chromosome 17 from 35.37 Mb to 36.06 Mb (*GSDM1*, *PSMD3*, *CSF3*, *MED24*, *SNORD124*, *THRA*, *NR1D1*, *TRNASTOP-UCA*, *MSL-1*, *CASC3*, *RAPGEFL1*, *WIPF2*, *CDC6*, *RARA*, *LOC100131821*, *GJD3*, *LOC390791*, *TOP2A*, *LOC728207*, *IGFBP4*, *TNS4*, *CCR7*, and *SMARCE1*). Sixteen of the 51 cell lines have *HER2* gene amplification, and five of these contain coamplification of *TOP2A*. As expected among these five cell lines, all 23 genes included in the *TOP2A* signature show increased copy number; however, there is substantial variability in their expression pattern among the cell lines (Figs 1A, 1B). Only three of the 23 genes demonstrated overexpression in all five *TOP2A*-coamplified breast cancer cell lines; six genes were overexpressed in four of these cell lines, two genes in three cell lines, five genes in two cell lines, and seven genes in only one cell line. We also found that 15 of the 23 genes in the *TOP2A* signature were amplified in one of the 11 breast cancer cell lines lacking *TOP2A* amplification but containing *HER2* amplification. Twelve of the genes in the *TOP2A* signature that are located centromerically to *TOP2A* (ie, toward *HER2*) were both amplified and overexpressed in at least one of the *HER2*-amplified breast cancer cell lines lacking *TOP2A* coamplification. This is expected given the well-documented variable size of the *HER2* amplicon. In addition, the variable pattern of expression among these 23 genes does not distinguish *HER2*-amplified, *HER2*/*TOP2A*-coamplified, or *HER2*/*TOP2A*-normal cell lines from one another (Fig 1A). Taken together, these data suggest significant variability in expression of the 23-gene *TOP2A* signature that is sometimes unrelated to *TOP2A* gene amplification.

The *TOP2A* signature was significantly associated with pathCR only in the *HER2*-positive as opposed to the *HER2*-negative subgroup. This is also expected, because *TOP2A* is amplified almost exclusively when *HER2* is amplified.²⁵ Indeed, *TOP2A* amplification, when present, is a coamplification event driven by the *HER2* amplicon.^{13–17,25–29} A stroma signature

Fig 1. Expression patterns for 23 genes composing topoisomerase II alpha (TOP2A) expression signature among breast cancer cell lines with HER2 (*ERBB2*) amplification. (A) Gene expression microarray heatmap of 23-gene TOP2A signature in 51 breast cancer cell lines. Raw gene expression microarray data adapted.²⁴ We used copy number data from single nucleotide polymorphism microarrays and expression data from microarray analyses for 51 breast cancer cell lines to evaluate association of gene amplification with overexpression for these 23 genes. Eleven breast cancer cell lines have HER2 but not TOP2A amplification, five cell lines have HER2/TOP2A coamplification, and 35 cell lines have neither HER2 nor TOP2A amplification. Red corresponds to increased expression, whereas green corresponds to decreased expression. Cell lines are listed on y-axis. Blue along y-axis indicates cell lines with TOP2A and HER2 coamplification. Orange along y-axis indicates cell lines with only HER2 amplification. Purple indicates cell lines that are HER2 and TOP2A normal. Genes in TOP2A signature are listed at top of figure according to their relative genomic position. HER2 is centromeric to 23 genes in TOP2A signature and is indicated to highlight its overexpression exclusively in HER2-amplified cell lines. (B) Frequency of overexpression relative to gene amplification was determined. Gold bars indicate cell lines that are TOP2A and HER2 amplified as well as coamplified for gene indicated on x-axis. Blue bars indicate cell lines that are TOP2A nonamplified and HER2 amplified, but amplified for gene indicated on x-axis. Percentage of cell lines with increased gene copy number that also had overexpression of referent gene is indicated on y-axis. Gene amplification was not consistently associated with overexpression of these 23 genes. In addition, some genes in signature are amplified and overexpressed in absence of TOP2A amplification (blue bars). Finally, several genes in TOP2A signature had increased expression in absence of amplification of TOP2A, HER2, and referent gene. Genes are listed according to their relative location, with genes toward left of graph centromeric and genes toward right of graph telomeric of one another. (*) Four or fewer cell lines showed overexpression of the gene in the absence of amplification.

resulting from an averaged sum of 68 genes, with *PLAU/uPA* as the prototype gene,¹² and an immune response signature made up of an averaged sum of 95 genes, with *STAT1* as the prototype gene,¹² were also evaluated by Desmedt et al.¹¹ Because these two other signatures were found by the authors to have some association with response to anthracyclines, these signatures were combined with the TOP2A signature to obtain the composite A-score, which the authors found to be more signif-

icantly associated with pathCR in these trials than any of the individual expression signatures.

This A-score provided a significant association with pathCR in a relatively small number of patients with ER-negative breast cancers who were evaluated in the study. However, the statistical power of this study to address the clinical utility of the A-score or of TOP2A gene amplification is limited. The reported trials are relatively small, indicating that these results

are preliminary and will require confirmation in larger studies. This is particularly true because Desmedt et al¹¹ as well as others^{17,25} have shown that *TOP2A* gene amplification is found in only approximately 9% of breast cancers. Again, this necessitates much larger studies to validate the potential role of the A-score in breast cancer treatment decision making.

Because essentially all breast cancers with *TOP2A* gene amplification also have *HER2* gene amplification, patients with these characteristics are candidates for trastuzumab or other *HER2*-targeted therapies, such as lapatinib. These efficacious drugs are offered to essentially all patients with *HER2*-positive breast cancer in North America and throughout many other parts of the world. In this context, one might question if there is any role for the A-score or for any other predictive marker of anthracycline responsiveness or resistance, such as *TOP2A* gene amplification. We, like Desmedt et al,¹¹ believe predictive markers for anthracyclines (or *TOP2A*-targeted therapeutic agents) are still relevant. Anthracycline-based chemotherapy currently is a component of most breast cancer adjuvant regimens. Treatment outcomes (disease-free and overall survival) from studies comparing anthracycline-based chemotherapy alone in women whose breast cancers have *HER2/TOP2A* coamplification are not significantly different from those with trastuzumab-containing treatments.^{17,30} This observation has been made in two different randomized clinical trials: one of trastuzumab in women with metastatic breast cancer¹⁷ and one of trastuzumab in the adjuvant setting (BCIRG [Breast Cancer International Research Group] 006).^{17,30} Because trastuzumab substantially adds to the cost of any chemotherapy regimen, physicians in some countries may wish to identify the subgroup of patients with *HER2*-positive breast cancers that are coamplified for *TOP2A*, given the comparable treatment benefit from anthracycline-containing chemotherapy alone. This would result in a substantial reduction in the cost of adjuvant chemotherapy that the addition of trastuzumab brings to the regimen. Again, this is particularly important in locations where cost of therapy limits availability of the targeted agents. For patients in these areas, it would be important to know whether the use of anthracyclines, with their potential attendant long-term toxicities of leukemia, myelodysplasia, and congestive heart failure, would add any incremental benefit over nonanthracycline regimens.³¹⁻³³

There has been a long-standing need for predictive markers for chemotherapy agents, especially agents like anthracyclines that have substantial short- and long-term toxicities. The use of gene signatures has demonstrated potential for addressing some of this need; however, it remains to be seen if predictive signatures of the complexity of the A-score can be validated in other studies and reduced to practice on a broader basis. In the case of anthracycline sensitivity, it is not yet clear that such signatures are really more useful than single markers such as *TOP2A* amplification, which has been reported to be useful when tested with carefully validated cutoffs combined with reproducible methodology for defining marker-positive and marker-negative cancers.^{17,30} This may well be the situation in identifying those few breast cancers that incrementally benefit from anthracycline-based therapies. It is not always the case that more is better. Indeed, in some instances, less can be more.

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