Updates on Adjuvant Therapy for Early Stage Hormone Receptor-Positive Breast Cancer

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Abstract

Optimization of adjuvant systemic therapy in women with early-stage hormone receptor-positive breast cancer includes the consideration of chemotherapy and ideal type and duration of anti-hormone therapy. The use of gene expression profiling as a predictive marker for determining benefit to chemotherapy has become an important consideration when recommending chemotherapy in patients with early stage hormone receptor-positive breast cancer. Recent results from the TAILORx and MINDACT studies provide the first prospective data, designed to give more conclusive guidance on assays. Defining the optimal adjuvant anti-hormone therapy, administered after the consideration of chemotherapy, is a constantly evolving field, in which factors such as menopausal status, drug type, and duration of therapy are carefully considered. New data from the MA17R study and the 2016 San Antonio Breast Cancer Symposium (SABCS) provide early evidence that demonstrates the benefit of extending the duration of aromatase inhibitors builds on previous studies investigating extended tamoxifen or sequential therapies between these 2 drug classes. Indeed, modern breast oncology care for patients with early stage hormone receptor-positive disease involves individualizing recommendations based on clinical presentation and genomic assays to provide optimal chemotherapy, and anti-hormone regimens. This manuscript will provide updates on approaches to gene expression analysis and extended aromatase inhibitors in early breast cancer, focusing on several recent presentations and publications.

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Adjuvant Chemotherapy in Hormone Receptor-Positive Disease: To Give or not to Give

Chemotherapy in Hormone Receptor-Positive Disease
Adjuvant chemotherapy for early-stage breast cancer was first described in the 1970s,[1] with systemic cytotoxic chemotherapy demonstrating an improvement in survival in patients with early stage disease. Although adjuvant chemotherapy may benefit some patients, not all patients with breast cancer derive a benefit.[2] Thus, the decision to prescribe adjuvant chemotherapy is a crucial one, and while certain pathologic markers can help assess the likely benefit from systemic cytotoxic therapy, genomic assays have been studied to help predict those patients most likely to benefit from treatment.[3]

Gene expression microarrays have been used to define specific subtypes of breast cancer.[4] These include basal-like, HER2-positive, normal breast-like, and luminal epithelial categories.[4] The luminal subtypes are generally associated with the estrogen receptor (ER) and progesterone receptor (PR); however, not all ER-positive tumors behave similarly.[5] Molecular analysis of the luminal subtypes can categorize them as luminal A and B, which behave as distinct phenotypic entities, with luminal B tumors demonstrating higher histologic grade, Ki67, and an increased risk of relapse compared to luminal A tumors.[4-6] Rapidly dividing cells, as compared with more indolently dividing cells, tend to be more sensitive to chemotherapy; thus, surrogate pathological markers of rapidly dividing tumors include higher histologic grade and Ki67.[7] Understanding which tumors exhibit a more aggressive phenotype can help identify which are more likely to benefit from cytotoxic chemotherapy. Gene expression assays such as PAM50 can estimate these intrinsic subtypes of breast cancer and categorize them by cumulative risk of recurrence and death.[8]

Although PAM50 subtypes have prognostic value in breast cancer, this molecular profiling technique has not been validated as a predictive marker of response to therapy. Although there exists various gene expression assays that may hold prognostic and/ or predictive value, the two assays that have been most rigorously validated and most commonly used in practice are the Oncotype Dx and Mammaprint assays. This review will focus on recent updates of the Oncotype Dx and Mammaprint assays from recent publications, and their implications for practical use when deciding adjuvant chemotherapy for early-stage hormone receptor-positive breast cancer.

Oncotype Dx
The Oncotype Dx recurrence score (RS) is based on a 21-gene assay,

which includes numerous genes involved in breast oncogenesis and proliferation. Initial retrospective studies using tissue data from NSABP B-14, which randomized ER-positive node-negative patients to 5 years of tamoxifen or no therapy, validated the RS could predict distant recurrence.[9] Results from NSABP B-20, which randomized ER-positive node-negative patients to cyclophosphamide, methotrexate, and 5-fluorouricil, has been used to retrospectively validate the ability of Oncotype Dx to predict the magnitude of benefit from adjuvant chemotherapy using cut offs for low, intermediate, and high scores (< 18, 18-30, ≥ 31; respectively).[3] In the clinical setting, patients with low scores typically would not be recommended chemotherapy, whereas patients with high scores would; the challenge has been in deciding on the benefit of chemotherapy in patient with intermediate scores. In order to address how to approach intermediate scores and prospectively validate the Oncotype Dx assay, the Trial Assigning IndividuaLized Options for Treatment (TAILORx) study was designed in node-negative patients, and the Treatment for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER) study was designed in node-positive patients. The TAILORx study determined the RS in patients with node-negative ER-positive breast cancer, if they have a low score (defined as 0 to 10) patients proceed with endocrine therapy and omit chemotherapy. If they have a high score (greater than 25) patients proceed with chemotherapy followed by endocrine therapy; however, if they have an intermediate score (11 to 25) they are randomized to receive chemotherapy or not. Results thus far have been published for patients with a low RS, and as anticipated, these patients have favorable outcomes with disease-free survival (DFS) of 93.8% at 5 years (95% Cl, 92.4-94.9).[10] The study has not yet reported outcomes on the subgroup of patients with intermediate scores. In addition, results from the RxPONDER study will provide much needed data for chemotherapy decisions regarding the node-positive group. The study is designed to randomize patients with node positive ER-positive breast cancer with an RS of 25 or less to receive chemotherapy and hormone therapy versus hormone therapy alone.[11] While Oncotype Dx is not considered a standard of care in node-positive patients, retrospective analysis from SWOG 8814, which tested the addition of anthracycline-based chemotherapy to tamoxifen in postmenopausal ER-positive node-positive women, found significant survival benefit of chemotherapy in tumors with a high Oncotype Dx score (> 31), but no significant benefit in those with low scores, <18.[12]

While the Oncotype Dx RS can provide a perspective on disease biology and chemosensitivity, studies have demonstrated that a simple validated model based on routine pathologic markers (ER, PR, grade, Ki67) correlates very closely with the Oncotype score.[13] Indeed, other assays, such as the IHC4 have used algorithms based on routine pathological markers, and can strongly predict recurrence rates and may also be helpful in determining benefit from chemotherapy.[14]

MINDACT

Mammaprint is a 70-gene gene-expression assay correlated with six hallmarks of oncogenesis: evading apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, limitless replication, tissue invasion and metastasis, and angiogenesis.[15] Mammaprint provides a raw score which classifies tumors into low- and high-risk based on distant recurrence risk at 5 and 10 years, and has been validated as prognostic.[16]

The MINDACT trial was a phase 3 study in patients with early breast cancer where the primary endpoint was to assess if patients with high risk based on clinical assessment (using a modified version of Adjuvant! Online) and low genomic risk (using MammaPrint), benefited from adjuvant chemotherapy after randomization.[17] Chemotherapy regimens patients received included anthracycline-based chemotherapy or docetaxel with capecitabine; anthracycline regimens including taxanes were not used. Among the total of 6693 patients enrolled, 23% (n = 1550) had high clinical risk and low genomic risk. These patients underwent randomization to chemotherapy (n = 1497) versus no chemotherapy, of which 82% (n = 1228) were evaluable per protocol. The rate of DFS at 5 years for those who did not receive chemotherapy was 94.7% (95% CI, 92.5-96.2) and 95.9% (95% CI, 94-97.2) in those who did receive chemotherapy; a statistically non-significant 1.5 percentage point difference (HR, 0.78; 95% CI, 0.50-1.21; *P* = .27). Since the study met its primary endpoint, these results suggest that patients with high clinical risk and low genomic risk do not benefit from chemotherapy. Subset analysis also found this to be the case whether patients were node-negative or node-positive. Results for the low clinical risk and high genomic risk group showed a 5-year rate of survival without distant metastasis of 95.8% (95% CI, 92.9-97.6) among those who received chemotherapy, as compared with 95% (95% CI, 91.8-97) who did not receive chemotherapy (HR, 1.17; 95% CI, 0.29-2.28; *P* = .66). While this was not the primary objective of the study, this infers that patients with low clinical risk may not require additional testing as even those with a high score did not experience a differential benefit to adjuvant chemotherapy.

There are important limitations to consider in this study which may restrict its generalizability. For instance, the study enrolled a heterogeneous population, which included 9.5% patients with HER2-positive breast cancer, and 9.6% with triple-negative breast cancer. The ER-negative cohort was too small, comprising only 11.6% of all patients, and these results cannot be extrapolated to these patients. Moreover, because the original sample size calculations were based on the total number of patients, the inclusion of ER-negative patients reduces the sample size of the ER-positive cohort, which could reduce the power to interpret results. Furthermore, 21% of patients had node-positive disease, limiting conclusions related to this subset. Therefore, these data provide evidence primarily for patients with ER-positive, node-negative disease. Clinical risk was assigned using Adjuvant! Online which does not factor in all pathological variables that contribute to risk such as

PR and Ki67; indeed, it is currently offline because it is undergoing updates. Finally, while the main analysis found a statistically non-significant benefit of 1.5% favoring the chemotherapy arm it is important to consider that patients were administered second generation chemotherapy regimens (either anthracycline-based or docetaxel and capecitabine). The benefit of adding a taxane to anthracycline-based regimens has been demonstrated in numerous studies, and it is unknown if third-generation regimens in patients with Mammaprint low scores with high clinical risk would have a similar rate in DFS.[18]

Practical Guidance of Gene Expression Platforms
Both Oncotype DX and Mammaprint are FDA approved genomic assays which can be used to guide adjuvant chemotherapy treatment decisions, each with its own limitations. The design of MINDACT couches the interpretation of Mammaprint in clinical risk, and lends itself to practical application in the setting of high clinical risk. Studies investigating Oncotype DX on the other hand are not couched in clinical risk; rather the decision to give adjuvant chemotherapy or not depends solely on the molecular platform. The initial results of the TAILORx study, however, demonstrate that patients who have a low RS do exceedingly well and chemotherapy can be omitted with confidence. These different setting in which the assays have been studied and developed may help guide selection of which assay to order in clinic. However, they should be ordered when their results may affect clinical decision making, and it is important to factor in patient and tumor characteristics, as well as patient preference, on an individual level.

Approach to Adjuvant Endocrine Therapy in Postmenopausal Women: Is Longer Duration Better?
Experience with Anti-Hormone Therapy in Early Breast Cancer
Anti-hormone drugs were the first targeted therapy in oncology and have become a cornerstone of treatment in hormone receptor-positive breast cancer.[19] Tamoxifen, a selective ER modulator (SERM), was the first anti-hormone therapy approved for the adjuvant treatment of breast cancer.[20,21] When compared to no endocrine therapy in the adjuvant setting, the use of tamoxifen for 5 years significantly reduces the risk of breast cancer recurrence.[22] Following this significant breakthrough, a more potent class of anti-hormones, the aromatase inhibitors (AI), were found to be superior to tamoxifen in postmenopausal women, with improvements in recurrence rates.[23] The natural history of hormone receptor-positive breast cancer demonstrates that these types of breast cancers can recur years or even decades after initial diagnosis, suggesting that extended regimens may be helpful.[24] Because of the superiority of AIs and the risk of late recurrences, several adjuvant studies have also looked at sequential administration of tamoxifen and AIs in postmenopausal patients, evaluating varying sequences and duration of therapy (**Table 1**). Furthermore, data investigating extended regimens of tamoxifen have found an improvement in

DFS and OS, leaving the question if extended AIs would have similar benefits.[25,26] This review will focus on the recent publication of the MA-17R and presentations of the DATA, IDEAL, and NSABP B-42 studies at the San Antonio Breast Cancer Symposium (SABCS), which investigate various approaches to extended AI therapy.[27]

MA-17R
In the MA-17R studied patients who had finished 5 years of letrozole after having received tamoxifen (median duration of 5 years, with 68.5% of patients receiving tamoxifen for 4.5 to 5.5 years) who were randomized to receive another 5 years of letrozole versus placebo.[27] This study achieved its primary endpoint as it found that extending letrozole for an additional 5 years increased the 5-year DFS rate from 91% to 95%, (HR, 0.66, 95% CI, 0.48-0.91; $P = .01$).[27] The majority of the benefit observed was in preventing ipsilateral loco-regional or contralateral breast cancer recurrence with the extension of letrozole versus placebo (3.3% versus 6.4%, respectively); however the incidence of distant recurrence was similar between both arms (4.4% versus 5.5%, respectively).

Authors noted that the extension of treatment with letrozole lead to a statistically significant worsening of bone density. This was in the context of a greater rate of clinical fractures observed in those taking extended letrozole (14% versus 9%; $P = .001$, respectively). Furthermore, although overall quality-of-life assessments were not significantly different between study arms, there were significant in between-group differences over time for bodily pain and the role-emotional subscales ($P = .03$ and $P = .03$, respectively). In interpreting these data, it is important to consider that this trial selected a population of patients that were already very familiar with, and likely tolerant of, the side effects of anti-hormone therapy. Additionally, extended courses of anti-hormone therapy are typically associated with suboptimal adherence, indeed MA-17R found adherence rates of 62.5% among those receiving letrozole and 62.3% for placebo.

SABCS 2016: First Results of DATA, IDEAL, and NSABP B-42
More recently at the 2016 SABCS, several studies have reported on extended durations of AI therapy (**Table 1**). The DATA study randomized 1912 postmenopausal women who had received 2 to 3 years of tamoxifen versus 6 years of anastrozole. The study did not meet its primary endpoint as 5-year DFS was 83.1% in the 6-year group, and 79.4% in the 3-year group (HR, 0.79; 95% CI, 0.62-1.02, $P = 0.07$).[28] There was some benefit in higher risk groups of patients including those with larger tumors and those which were node-positive. Given the biology of ER-positive breast cancer, these are early data and longer follow up is required. The IDEAL study randomized patients who had completed 5 years of endocrine therapy (either 5 years of tamoxifen or AI, or tamoxifen followed by AI) to an additional 2.5 versus 5 years of letrozole.[29] There was no significant difference in 5-year DFS

(88.4% versus 87.9%; HR, 0.88; 95% CI, 0.64-1.21, P = .43), however, these are relatively early data as well and longer follow up is required. The NSABP B-42 study investigated postmenopausal women who had completed 5 years of endocrine therapy (either 5 years of AI or tamoxifen followed by AI) to 5 years of letrozole versus placebo.[30] Again in this study there was no statistically sig-nificant difference in DFS (81.3% versus 84.7%; HR, 0.85; 95% CI, 0.73-0.999; P = .048 where significance level at .0418), again, longer follow up is needed. While these studies did not meet their primary endpoints, these data need to mature, as benefit with extended adjuvant endocrine therapy is typically observed beyond 9 years.[25,26]

TABLE 1. Hallmark Trials for Adjuvant Anti-Hormone Therapy in Postmenopausal Women.

Anti-hormone therapy	Study	Duration/Sequence	ER-positive patients (n)	Disease Free Survival
Tamoxifen	ATLAS[25]	5 vs 10 years of tamoxifen	6846	79.2% vs 82.01% HR, 0.90 for yrs 5 to 9 (95% CI, 0.79-1.02). HR, 0.75 for >9 yrs (95% CI, 0.62-0.90)
	aTTom[26]	5 vs 10 years of tamoxifen	2755	80.8% vs 83.3% HR, 0.99 at yrs 5-6; (95%CI; 0.86-1.15). HR, 0.84 at yrs 7-9; (95% CI, 0.73-0.95). HR, 0.75 at > 9 yrs; (95%, CI 0.66-0.86 P = .003
AI	BIG-1-98[34]	5 years tamoxifen vs 5 years AI	6686	81.4% vs 84% HR, 0.81 (95% CI, 0.70-0.93; P = .003)
	ATAC[35]	5 years tamoxifen vs 5 years AI	7839	87.4% vs 89.4% HR, 0.83 (95% CI, 0.71-0.96; P = .013)
	IES[36]	Tamoxifen x 2-3 years → tamoxifen vs AI for total 5 years	3853	86.8% vs 91.5% HR,0.68 (95% CI, 0.56-0.82; P <.001)
	Italian study[37]	Tamoxifen x 2-3 years → tamoxifen vs AI for total 5 years	397	85.8% vs 94.6% HR, 0.35; (95% CI, 0.18-0.68; P = .001)
	MA-17[38]	Tamoxifen x5 years → placebo vs AI x5 years	5048	87% vs 93% HR, 0.57 (95% CI, 0.43-0.75; P = .00008)
	MA-17R[27]	Tamoxifen for any period → AI x5 years a placebo vs AI x 5 years	1895	91% vs 95% HR, 0.66 (95% CI, 0.48-0.91; P = .01)
Combinations	DATA[28]	Tamoxifen 2-3 years → 3 vs 6 years of AI	1912	79.4% vs 83.1% HR, 0.79 (95% CI, 0.62-1.02; P = .07)
	IDEAL[29]	Endocrine x5 years → 2.5 vs 5 years AI	1824	87.9% vs 88.4% HR, 0.88 (95% CI, 0.64-1.21; P = .43)
	NSABP B-42[30]	Endocrine x5 years → placebo vs AI x5 years	3966	81.3% vs 84.7% HR, 0.85 (95% CI, 0.73-0.999; P = .048 where significance level at .0418)

Practical Guidance of Gene Expression Platforms and Future Directions
Studies investigating extended AI therapies are showing modest to no benefit thus far, therefore, decisions to extend AI therapy beyond 5 years should be done on an individual basis, considering patient and tumor characteristics and toxicity. Since the majority of benefit is in chemoprevention, the patient's desire and eligibility for chemoprevention should be discussed. Patients with bilateral mastectomies for instance, would be less likely to benefit from chemoprevention. In addition, AIs are not benign medications, and these studies have demonstrated the significant effect on bones and certain quality-of-life measures, therefore, considering bone health as well as other side effects patients may be experiencing should weigh in on the decision. Subgroup analysis from the DATA trial suggest that there may be greater benefit in patients who are at high risk as deemed by tumor size of presence of lymph node metastasis, and this may be the group that is most likely to benefit. However, while the concept that higher risk groups may benefit from longer therapy is reasonable, the fact that the benefit may be modest suggests there are other mechanisms at play. Indeed, mutations of *ESR1* and the *PI3K* pathway have been implicated in resistance in a subset of hormone receptor-positive breast cancers.[31,32] Ultimately targeting resistance mechanisms in defined subsets of hormone receptor-positive breast cancer may be more important than longer duration of endocrine therapies.

Conclusion
A better understanding of disease biology has led to these state of the art approaches to adjuvant therapy. Both the Oncotype Dx and Mammaprint now have prospective data to support their use in clinical practice, albeit with their own set of limitations. They can nevertheless be helpful in patients with hormone receptor-positive and node-negative disease. These tests need to be considered in clinical context, and decisions to order and apply them evaluated on an individual basis. Studies such as the OPTIMA trial are comparing Mammaprint, Oncotype DX, PAM50, the IHC4 and various other assays, and will provide information as to how these assays perform against each other.[33] In terms of optimizing anti-hormone therapy in postmenopausal women, evidence suggests that extended anti-hormone therapies may provide modest protection against breast cancer recurrence; however, this is not necessarily required for all patients, and decisions should be individualized. As we push the boundaries with state of the art molecular biomarkers and treatment strategies, we have continued to make incremental improvements to patients care; however, more research understanding breast cancer biology and molecular mechanisms of resistance are needed to further optimize care.

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