

The Natural History of Hormone Receptor-Positive Breast Cancer

Abstract: Approximately 70% of human breast tumors express hormone receptors (HRs), comprising the estrogen receptor (ER) and/or progesterone receptor (PR). The ER is the primary transcription factor driving oncogenesis in HR-positive (HR+) breast cancers; it is both a target of, and predictor of response to, anti-estrogen therapy. Unlike in other breast cancer subtypes, more than half of all disease recurrences in HR+ breast cancer occur 6 years or more after diagnosis, particularly following 5 years of adjuvant anti-estrogen therapy. Late relapses in HR+ breast cancer thus represent a significant clinical challenge. There is considerable molecular and clinical heterogeneity underlying HR+ breast cancers, and a limited understanding of the mechanisms underlying treatment resistance and late relapse. In this review, we describe the long natural history of HR+ breast cancer and discuss relapse patterns in relation to their clinicopathological and molecular characteristics. We highlight the relationship between tumor relapse and anti-estrogen therapy resistance, and we describe the concept of tumor dormancy. Finally, we review novel translational research strategies utilizing preclinical models and patient tumor samples, and current clinical strategies that address this increasingly common challenge in breast cancer.

Introduction

Approximately 70% of human breast tumors express hormone receptors (HRs)—the estrogen receptor (ER) and/or the progesterone receptor (PR); these are the primary transcription factors driving oncogenesis in HR-positive (HR+) breast cancers. Both are targets of and predictors of response to anti-estrogen therapy.[1,2] Upon stimulation by estrogen, ER is recruited to specific sites across the genome in a highly organized manner through specific epigenetic events that restrict its recruitment to a subset of its potential binding sites.[3] ER signaling can be effectively targeted by antagonizing the binding of estrogens to the

ER with tamoxifen, blocking estrogen biosynthesis with aromatase inhibitors (AIs) and luteinizing hormone-releasing hormone (LHRH) agonists, and down-regulating ER with fulvestrant (Faslodex). However, a significant minority of patients relapse despite adjuvant anti-estrogen therapy. Most patients with metastatic disease ultimately develop resistance to anti-estrogen therapies. HR+ tumors do not represent a single disease entity, and there is considerable molecular and clinical heterogeneity.[4] Unlike other breast cancer subtypes, HR+ breast cancer is commonly associated with late recurrences,[1,5,6] with an annual risk of distant recurrence following ad-

juvant anti-estrogen therapy of 1% to 4%, depending on the extent of initial disease.[7] The use of adjuvant AIs and the addition of chemotherapy to anti-estrogen regimens may benefit some patients,[8,9] but these seem to have little impact on the risk of late recurrence.[10] At present little is known about the predictive markers for late relapse and underlying mechanisms of treatment resistance and late relapse, for which alternative treatment strategies are clearly required. In this article, we describe the long natural history of HR+ breast cancer and review current research and clinical strategies to address this clinical challenge.

Heterogeneity of Luminal Breast Cancer and Determinants of Prognosis and Biological Behavior

Classic clinicopathological factors such as tumor size, nodal status, histological grade, and human epidermal growth factor receptor 2 (HER2) co-expression are important predictors of patient outcome and are commonly factored into treatment algorithms for HR+ tumors, but their relationship to relapse patterns is less clear. A retrospective analysis of 3,000 patients with early-stage breast cancer demonstrated that larger tumor size predicted for both early recurrences (0 to 5 years after diagnosis) and late recurrences (5 to 12 years after diagnosis), but did not predict for late recurrences when controlled for nodal status.[6] In contrast, nodal involvement was a good predictor of both early and late recurrences. Although tumor burden is incorporated in prognostic tools such as Adjuvant! Online ([¹Division of Women's Cancers, Dana-Farber Cancer Institute, Boston, Massachusetts](https://www.adju-</p></div><div data-bbox=)

vantonline.com), current clinical and molecular tools generally select for relapse primarily in the first 5 years and not for late relapse.[5] Another retrospective analysis of 400 patients found no association between histological grade and time of relapse.[5] In a meta-analysis of 10,000 patients, HER2 and HR coexpression was associated with poorer outcomes than HR+, HER2–non-amplified (HER2–) tumors.[11]

Invasive lobular carcinoma (ILC) represents the second most common breast cancer histological subtype, accounting for 10% to 15% of breast cancers, and the vast majority express HR. ILC differs from invasive ductal carcinomas (IDCs) with respect to epidemiology, clinicopathological features, and natural history.[12] In early-stage breast cancer, patients with ILC have a better overall survival (OS) in the first 10 years after diagnosis compared with those who have IDC, but the opposite was observed with longer follow-up.[13] It is unclear whether these observed differences in the natural history can be explained solely by differences in histology, or whether they are influenced by the different distribution of molecular subtypes.

Molecular subtyping of breast cancer represents a major advance and includes at least two luminal subtypes (luminal A and B), each with distinct pathological characteristics and disease outcomes.[4] Luminal A tumors are characterized by ER-regulated genes and better outcomes, while luminal B tumors have higher genomic grade values and are associated with poorer outcomes.[14] Several multigene expression signatures and PAM50, a multi-gene expression signature using reverse transcriptase polymerase chain reaction (RT-PCR) to classify breast tumors into their major “intrinsic” subtypes,[15] have been shown to provide prognostic value in early-stage breast cancer beyond traditional clinicopathological risk assessment.[16,17] These include Oncotype DX

(Genomic Health),[8] MammaPrint (Agendia),[18] and Genomic Grade Index (Ipsogen),[19] which also provide additional information on the benefit of chemotherapy in early-stage breast cancer.[16] The common denominator in these multigene signatures is the inclusion of proliferation genes in their indices,[8,16] and they tend to identify patients at higher risk of early relapse.[5] The combination of Ki67, HR, and HER2 expression have been used by some groups as an immunohistochemistry (IHC)-based surrogate for the molecular subtypes, with variable cutoff points for Ki67 proposed to differentiate between the low-proliferation luminal A and the high-proliferation luminal B tumors.[20] A retrospective analysis of 2,000 patients with node-negative breast cancer from two phase III trials at a median follow-up of 13 years found that while patients with both IHC-defined luminal A and B tumors had a persistently elevated risk of late recurrence over time, patients with luminal B tumors had higher distant recurrence rates and significantly worse survival outcomes compared with those who had luminal A tumors.[21] Therefore, both luminal A and B subtypes contribute to early and late recurrences, and there are few data to support the common assumption that luminal B tumors relapse early and luminal A tumors relapse late.

Relapse Patterns in Relation to Anti-Estrogen Resistance and Tumor Dormancy

Patients with HR+ tumors are at continued risk of relapse for many years after their initial breast cancer diagnosis. This clinical behavior is not unique to HR+ tumors; it is also seen in B-cell lymphoma, melanoma, prostate cancer, and renal cell cancer.[22] Among women treated with tamoxifen for 5 years, more than half of all recurrences occur between 6 and 15 years after diagnosis.[1] In a meta-analysis of 10,000 patients, HR-negative (HR–)

tumors were found to have a poorer prognosis in the first few years after diagnosis, but after 5 to 10 years, HR+ tumors were associated with relatively poorer outcomes.[11] Similarly, a combined analysis of 9,000 patients with node-negative disease found that patients who did not receive adjuvant therapy had a higher risk of recurrence 48 months after diagnosis if they had HR+ tumors rather than HR– tumors.[23] In patients with HR+ breast cancer treated with tamoxifen, the risk of relapse exceeded that of HR– breast cancer after 5 years, and chemotherapy benefit was primarily in the earlier period. These findings are concordant with the overview data from the Early Breast Cancer Trialists Collaborative Group (EBCTCG).[1,2]

In thinking about the relapse patterns of HR+ breast cancer, it is important to consider its relation to anti-estrogen resistance and tumor dormancy, as the mechanisms underlying these two processes may be quite different (Figure). Resistance to anti-estrogen therapies can occur *de novo* (primary resistance) or be acquired (secondary resistance), and is likely a major cause of early relapse during adjuvant anti-estrogen therapy, and during progressive disease in metastatic breast cancer. Anti-estrogen resistance occurs despite continued expression of the ER, and the signaling pathways regulating this are thought to involve a complex signaling network that is poorly understood.

Tumor dormancy is a term used to describe subclinical residual disease, which typically either remains undetected or relapses after a long interval period (Figure).[24] The regulation of the switch from quiescent dormancy to active regrowth in metastatic sites is poorly understood and likely includes interactions with host immunity and the metastatic niche.[22] The bone marrow is a common homing organ for breast cancer metastases and dormant breast tumor cells. In a large pooled analysis of 4,700 patients with

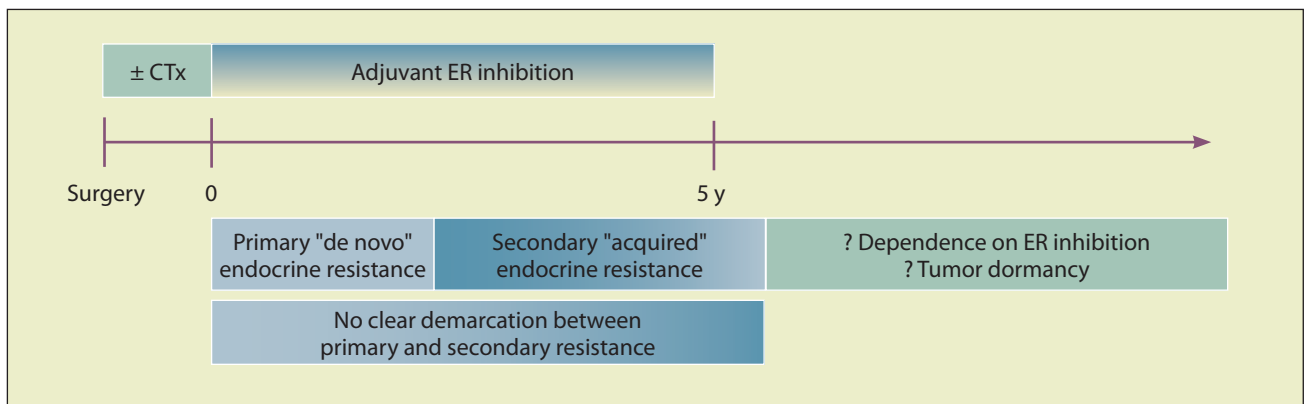


Figure: Conceptual Model of Luminal Breast Cancer Patterns in Relation to the Underlying Biology. CTx = chemotherapy; ER = estrogen receptor.

clinical stage I-III breast cancer who had screening bone marrow aspirates, a surprisingly large proportion (approximately 30%) of patients with HR+ tumors had micrometastatic bone marrow tumor involvement.[25] The primary tumors were larger and associated with a higher histological grade and nodal involvement. Bone marrow micrometastases were a predictor of poor outcome on multivariate analysis, and correlated with subsequent bone metastases and overt metastasis to viscera and brain. The incidence of bone marrow micrometastases was significantly lower in another study of patients with early-stage breast cancer by the American College of Surgeons Oncology Group (3% positive in 3,413 bone marrow specimens analyzed), but as in the above study, the presence of bone marrow micro-metastases was associated with decreased survival.[26]

The quantification of circulating tumor cells (CTCs) represents an area of active research as a marker of prognosis and treatment response.[24] In a study of 36 patients with no clinical evidence of breast cancer for 7 to 22 years following mastectomy, IHC-detected CTCs were found in a third of patients. As CTCs have a limited lifespan in circulation, these findings suggest the presence of a metastatic niche that gives rise to these cells.[27] As these patients may remain clinically disease-free for

long periods, there is likely a homeostatic mechanism maintaining the balance between tumor replication and cell death that replenishes the CTCs at a subclinical level.[22] In some patients, this balance keeps the dormant tumor cells in check for their entire life.

Clinical Strategies to Prevent Relapse

Current standard of care: adjuvant anti-estrogen therapy

The long-term benefits of 5 years of adjuvant tamoxifen use continue to show improvement over time. In the latest EBCTCG analysis, the absolute reduction in breast cancer mortality with 5 years of adjuvant tamoxifen continued to increase over time, and was about three times greater at 15 years after diagnosis than at 5 years after diagnosis. [1] The current clinical recommendation is that any positive level of ER expression is considered sufficient to justify adjuvant anti-estrogen therapy[28]; therefore 5 years of tamoxifen is the standard of care in the adjuvant treatment of HR+ breast cancer in premenopausal women.[29] This recommendation is based on retrospective analyses using older methods of ER assessments demonstrating that patients with tumors expressing low levels of ER appear to obtain some degree of benefit from tamoxifen.[1,30] A recent retrospective analysis of the National

Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial comparing patients with HR+ tumors who received a 5-year course of tamoxifen or placebo, found that patients whose tumors had the highest tertile of quantitative ER mRNA expression by RT-PCR had the highest distant recurrence-free survival at a median follow-up of 10 years, while the group with the lowest tertile fared far less well (hazard ratios [HRs] = 0.39 and 1.2, respectively).[31] In light of the potential toxicities with the long duration of adjuvant anti-estrogen therapies, many clinicians appropriately question the degree of benefit in patients with low levels of ER expression.

More recently, a number of well-conducted randomized trials have provided clear evidence of benefit of adjuvant third-generation aromatase inhibitors (AIs), such as anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin), compared with tamoxifen in postmenopausal women. These trials have typically been of 5 years' duration, with tamoxifen in the control arm, and either an AI or a sequential combination of tamoxifen followed by an AI in the other arm. A meta-analysis of these trials reported a lower recurrence rate with AIs than with tamoxifen, either when used upfront or following 2 to 3 years of tamoxifen, with an absolute benefit

of approximately 3% at 5 years.[9] The absolute difference in OS was minimal at a median follow-up of 5.8 years, and longer-term follow-up is required to determine whether there will be a more substantial benefit. In the 10-year analysis of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, which compared 5 years of adjuvant anastrozole vs tamoxifen, the annual HR of recurrence was 2% to 3%, and consistent with the meta-analysis data, there was no significant survival advantage. [32] Interestingly, the absolute differences in time to recurrence between anastrozole and tamoxifen increased over time (2.7% at 5 years and 4.3% at 10 years), with the difference lowest in the first 2 years, compared with 0 to 5 years and more than 5 years following the start of therapy (HR = 0.68, 0.77, and 0.81, respectively). The additional benefit of anastrozole beyond that achieved with tamoxifen appeared to wane after 8 years, and the difference in annual HRs for recurrence between the two treatments was minimal after this time. Although the inclusion of an AI in the adjuvant therapy of postmenopausal women is the current standard of care,[29] in light of the relatively small benefits of AIs over tamoxifen, clinicians should be comfortable tailoring the choice of anti-estrogen therapy in postmenopausal women according to the patient's tolerance of the drug's side-effect profile, especially in patients with lower-risk disease.

Addition of chemotherapy to adjuvant anti-estrogen therapy

While it is clear that adjuvant chemotherapy does benefit a subset of HR+ breast cancer patients, the challenge has been in identifying the patient subgroup for which chemotherapy is most effective. The use of adjuvant chemotherapy with anti-estrogen treatment appears not to reduce the risk of late recurrence, as most of the benefit occurs during the first few years after diagnosis.[2] In deciding which patients

should be recommended for adjuvant chemotherapy, what ultimately matters is not the risk of recurrence but rather, the likely benefit from addition of chemotherapy. The EBCTCG overview did not identify a subgroup of patients with HR+ breast cancer who did not benefit from chemotherapy, but it is possible that this finding was influenced by limitations in HR testing and the lack of centralized review of ER and PR status.[2] Chemotherapy responsiveness is considered to be directly correlated with cell proliferation activity and inversely correlated with anti-estrogen responsiveness.[33] It is likely that both endocrine therapy responsiveness and chemotherapy responsiveness are independent but interrelated tumor characteristics that exist along a continuum. The 2011 St. Gallen Conference consensus panel concurred that the luminal A subtype was less responsive to chemotherapy than other subtypes, and no particular chemotherapy regimen was favored over others for luminal tumors.[34]

More recently, multigene prognostic signatures, derived from high-throughput analyses of clinically annotated tumor specimens for gene expression patterns, have identified subsets of patients with HR+ breast cancers who benefit from the addition of chemotherapy to endocrine therapy.[8,35] Importantly, these assays also identify subsets of patients who do not benefit from chemotherapy and therefore may be spared its toxicity. Both the 21-gene Oncotype DX and 70-gene MammaPrint multigene signatures were validated in retrospective datasets, and prospective validation of these two multigene signatures is underway. TAILORx (Trial Assigning Individualized Options for treatment ([Rx]) (ClinicalTrials.gov identifier NCT00310180) will study the utility of the Oncotype DX score to predict for chemotherapy benefit in the intermediate score range, while MIN-DACT (Microarray In Node-negative and 1-3 positive lymph node Disease

may Avoid ChemoTherapy) (ClinicalTrials.gov identifier NCT00433589) will study the outcomes of patients with discordant risk assessments when using the 70-gene expression signature of MammaPrint compared to using clinicopathological features with the Adjuvant! Online program.[36,37] The results from these large, well-designed prospective studies are eagerly anticipated, as they will shed light on the best strategies to individualize adjuvant treatment in luminal breast cancer.

Extended adjuvant anti-estrogen therapy

The timing and duration of adjuvant anti-estrogen therapy are potential areas for intervention in addressing the risk of late relapse in HR+ breast cancer. Extending the duration of adjuvant anti-estrogen therapy has, in some settings, clearly reduced the risk of recurrence in HR+ breast cancer. Three trials have compared 5 years of adjuvant tamoxifen vs 5 years of tamoxifen followed by an additional 3 to 5 years of an AI in postmenopausal women, demonstrating an improved disease-free survival with extended therapy (HR = 0.58 to 0.68).[7,38,39] Present trials comparing 5 vs 10 years of treatment aim to identify the optimum duration of adjuvant AI therapy. There is no standard treatment available to reduce late recurrence risk in women who remain premenopausal after 5 years of tamoxifen, and clinical trials have generally excluded this subgroup of patients. Our group at Dana-Farber is currently exploring the efficacy of 2 years of extended letrozole in combination with an LHRH agonist following 5 years of tamoxifen in premenopausal women with stage I-III

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node-positive disease (ClinicalTrials.gov identifier NCT00903162). Extended anti-estrogen therapy is not without toxicities, and as the annual recurrence risk is modest, there will be important quality-of-life tradeoffs if this approach ultimately proves beneficial. One potential strategy to minimize diminishment in quality of life is intermittent anti-estrogen therapy, which is under investigation in the International Breast Cancer Study Group (IBCSG) SOLE (Study of Letrozole Extension) trial (ClinicalTrials.gov identifier NCT00553410). In SOLE, postmenopausal patients with node-positive HR+ breast cancer who have completed 4 to 5 years of an adjuvant endocrine therapy are randomized to receive an additional 5 years of letrozole given either continuously or intermittently in a 9-months-on, 3-months-off fashion.

Insights from metastatic HR+ breast cancer

Given the heterogeneity of luminal breast cancer, it is not surprising that refinements to basic endocrine therapies have been largely unsuccessful to date. In anti-estrogen–resistant breast cancer, there is reciprocal cross-talk between ER and other signal transduction pathways, including those involving receptor tyrosine kinases and insulin-like growth factor. HER2, for example, can signal through nongenomic ER, and as a result, most HR+ HER2+ tumors are less responsive to endocrine therapy.[40] The combined targeting of both the ER and HER2 pathways is therefore a clinically reasonable approach in HR+ HER2+ tumors; however, these tumors comprise only about 8% of HR+ breast cancers. [11] Both trastuzumab (Herceptin) and lapatinib (Tykerb) have been tested in combination with AIs, with improvements in progression-free survival (PFS) but little impact on OS.

The phosphatidylinositol 3-kinase (PI3K) pathway is frequently hyperactivated and promotes anti-estrogen

resistance in HR+ breast cancer.[41] Two phase II clinical trials have demonstrated promising efficacy with the combination of everolimus (Afinitor), an inhibitor of the mammalian target of rapamycin (mTOR), which is downstream of PI3K, with tamoxifen[42] and with letrozole.[43] The first of these trials was conducted in patients with metastatic disease who had prior exposure to anti-estrogen therapy, and the second included patients with newly diagnosed HR+ breast cancer. In a phase III trial comparing exemestane plus everolimus vs exemestane plus placebo, the subset of patients who had received prior nonsteroidal AIs in the adjuvant or metastatic setting had a median PFS of 10.6 months with combination therapy vs 4.1 months with exemestane alone (HR = 0.36). Although these results are not achieved without toxicity, they represent an important step forward in the treatment of anti-estrogen–resistant HR+ breast cancer, and co-targeting the PI3K pathway in the adjuvant setting is an attractive strategy to improve outcomes if the side effect profile can be improved.

Research Strategies to Identify Mechanisms of Anti-Estrogen Resistance and Predictors of Relapse

Patient tissue–based research

The challenge of late recurrences and a relatively low annual recurrence risk in breast cancer is unique to the luminal cancer subtypes. Large patient databases and long-term follow-up of patients are required to identify patients at greatest risk of recurrence, and pooled analyses of large clinical trials and nontrial data repositories are needed. There is also the added challenge of identifying tumor blocks to elucidate the molecular differences between tumors that relapse early, relapse late, or do not relapse at all. An improved understanding of these differences will enable better prediction of early treatment failure, and will

guide the use of novel strategies specifically directed at preventing early and late relapse. Additionally, the study of paired primary and metastatic tumor tissue, through RNA and gene sequencing platforms, may provide valuable molecular insights by identifying genes and pathways involved in the development of anti-estrogen resistance, and those that predict relapse risk. The discrepancy rate in paired primary and metastatic cancers for ER expression ranges from 3% to 36%, and from 25% to 48% for PR expression.[44,45] The basis of HR discordance is not well understood, and possible hypotheses include the variability in testing procedures, particularly when paired tissues are not tested concurrently; deterioration of sample quality over time; heterogeneity in tumor samples and sampling variability; and phenotypic drift as a result of tumor progression and/or treatment. The latter is particularly relevant in the setting of effective anti-estrogen therapy, potentially resulting in the selection of a resistant clone that is not dependent on ER signaling. Most consensus statements recommend that metastatic tumors be biopsied to reassess tumor phenotype, and while it is not possible to perform a repeat biopsy on every patient, it should be considered. Additional research biopsies should also be considered at this time to facilitate future research.

Recent efforts at identifying predictors of late relapse include a study of women with early-stage HR+ breast cancer treated with tamoxifen and followed up for a minimum of 10 years, in which transcriptomic differences in the primary tumor tissues of patients with distant relapses occurring at 3 or fewer years from diagnosis were compared to relapses that occurred after 7 years. [46] There was an increased relative expression of ESR1, ESR2, EGFR, BCL2, and AR in the late recurrence group and increased expression of CALM1, CALM2, CALM3, SRC, CDK1, and MAPK1 in the early recurrence group.

A similar retrospective study was performed on patients with HR+ HER2–tumors who did not receive adjuvant therapy, comparing tumors from patients who relapsed after ≥ 7 years to patients who had not relapsed after 10 years. This study identified a 241-gene signature in the late relapse group using the nearest centroid algorithm.[47] While it did not have a high predictive value in a small validation dataset, the functional annotation of this signature showed activation of pathways related to inflammatory response and angiogenesis in the late-relapsing tumors. Another novel approach is the genome-wide mapping of ER binding sites using chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-seq) techniques in HR+ primary breast cancers and metastases. Anti-estrogen-resistant cancers were found to continue to recruit ER to chromatin, but in tumors that were likely to relapse, unique ER-binding regions were acquired and the reprogramming of ER dynamics was mediated by the forkhead box protein A1 (FOXA1), an important pioneer factor for ER-chromatin binding.[48] Gene signatures derived from the acquired ER regulatory regions associated with poor clinical outcome specifically predicted for clinical outcome in HR+ disease. These translational studies using new technologies provide us with a greater depth of insight into the underlying genomic differences between HR+ breast cancers that define differences in response to treatment and outcome; the challenge is to identify suitably large and appropriate cohorts to validate these hypotheses.

Finally, there are significant technical advances in assays to detect small numbers of nucleated blood or bone marrow cells at frequencies of 1 per 10^6 – 10^7 cells. Once extracted, these cells can be studied at a molecular or functional level through cell culture, and may provide a surrogate view of the metastatic tumor population, as

well as important insights into the mechanisms and patterns of disease recurrence in breast cancer.[24] Should CTCs accurately reflect the biological and molecular characteristics in metastatic and subclinical HR+ tumor populations, they would represent a valuable resource in the study of anti-estrogen sensitivity, resistance, and tumor dormancy.

Preclinical models for anti-estrogen resistance

Multiple preclinical models of anti-estrogen resistance have been developed in breast cancer cell lines, including long-term estrogen-deprived (LTED) or estrogen-independent cells as models for resistance to AIs, and tamoxifen- and fulvestrant-resistant models.[49,50] There are global similarities in gene expression between HR+ cell lines and patient tumor samples, thereby supporting the validity of this approach to studying underlying mechanisms of anti-estrogen resistance.[51] These approaches have led to the identification of genetic and epigenetic factors that regulate ER signaling and endocrine signaling, such as the forkhead box protein FOXM1, which is activated through an estrogen-response element located in its proximal promoter region. Silencing of FOXM1 results in a reduction in estrogen-induced proliferation and overcomes acquired tamoxifen resistance in HR+ breast cancer cells.[50] Another approach has been to obtain gene expression signatures using either anti-estrogen-resistant cell lines and/or patient data sets with disease outcome to predict for resistance to endocrine therapy. By comparing the profiles of LTED cells to their parental counterparts, gene signatures for estrogen-independent growth and MYC transcription factor activation (by gene set analysis) were found to predict for early recurrence following adjuvant tamoxifen therapy in a validation patient cohort. MYC may thus be a potential therapeutic

target in anti-estrogen-resistant breast cancer.[49] The same investigators also demonstrated evidence of hyperactivation of the PI3K pathway in preclinical LTED tumor models, and these cells were sensitive to both anti-estrogens and PI3K pathway inhibitions, thereby providing preclinical rationale for the simultaneous inhibition of these pathways. In spite of these insights, development of relevant preclinical models that accurately simulate patients' tumor biology remains a challenge.

Conclusions and Outstanding Questions

While much of the research and treatment focus has been on extending the duration of anti-estrogen therapy and adding chemotherapy to prevent relapse, these approaches are not without morbidity, and we need to focus on overtreatment as well as undertreatment. As with chemotherapy, efforts are required to identify additional biomarkers besides HR expression, to better select subsets of patients who would or would not benefit from anti-estrogen therapy. It remains impossible to predict whether an individual patient will benefit from endocrine treatment, and what the magnitude or duration of any benefit will be; better predictors of each patient's anti-estrogen responsiveness are clearly needed. Prolonged anti-estrogen therapy (or reinstatement of anti-estrogen therapy after a treatment-free interval) will almost certainly be beneficial for some patients, particularly those with highly endocrine-responsive disease. For other patients, however, extended therapy is insufficient, and it remains to be seen whether combining endocrine therapy with other targeted approaches would be beneficial. Such approaches will need to be informed by a more comprehensive understanding of the heterogeneity that underlies luminal breast cancer. Tumor dormancy remains an area of active investigation and may also shed light on ap-

proaches than can reduce the risk of late recurrence.

The path forward requires a comprehensive preclinical and translational approach, incorporating the elucidation of the biology of HR signaling, mechanisms of anti-estrogen resistance and tumor dormancy. Long-term clinically annotated patient cohorts and access to tumor samples are required to make headway into the understanding of late relapse. Finally, in collaboration with our patients, we need to develop a strategy of increasing rates of obtaining metastatic biopsies at critical time points, such as at tumor progression, and to incorporate novel technologies, such as the molecular and functional study of disseminated tumor cells, into our research armamentarium. ○

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THE LIM/METZGER-FILHO/WINER ARTICLE REVIEWED: G. NAGARAJ, M.J. ELLIS, C.X. MA

The Natural History of Hormone Receptor–Positive Breast Cancer: Attempting to Decipher an Intriguing Concept

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We commend Elgene Lim and colleagues for providing a comprehensive review on the natural history of hormone receptor–positive breast cancer, highlighting the molecular and clinical heterogeneity of this disease, gaps in our understanding of its underlying biology, and challenges in research and clinical practice. We echo the sentiment that progress in treatment of hormone receptor–positive breast cancer has been slow and the impact of newer endocrine therapy approaches, such as the introduction of aromatase inhibitors (AIs) in the adjuvant setting and extended adjuvant therapy, on relapse and survival has been modest. Additionally, despite progress in the molecular profiling of breast cancer and subclassification of ER-positive disease into luminal A and luminal B subtypes, existing molecular assays have not raised new therapeutic hypotheses. This was the hope with results from the large-scale genome-sequencing studies.[1] However, the tremendous amount of somatic derangement/mutations occurring in ER-positive breast cancer at

the genome-wide level and the relative rarity of incidence for most of the significantly mutated genes underscore the need for genetic profiling of thousands of carefully annotated specimens to make sense of the patterns of somatic derangement/mutations that are emerging.[1]

The model of tumor relapse in relation to anti-estrogen therapy presented by Lim et al (see the Figure in their article) provides a useful framework for categorizing tumors into subgroups based on clinical phenotypes. Rightfully, the authors state that there is no clear demarcation between primary and secondary resistance. We would like to emphasize the utility of the neoadjuvant endocrine therapy Ki67 biomarker strategy in this regard. Since endocrine therapy functions by inhibiting tumor cell proliferation, a viable strategy to quickly tease out at least some “de novo” resistant tumors after diagnosis is to assess tumor Ki67 labeling index, a marker of tumor cell proliferation, 2 to 4 weeks after neoadjuvant endocrine therapy. Reassessment of Ki67 and the calculation of the Preoperative Endocrine Prognostic Index (PEPI) on the surgical specimen following 3 to 4 months of endocrine therapy provide further information about the endocrine responsiveness of the tumor.

As shown in the two neoadjuvant endocrine trials in postmenopausal women with early-stage breast cancer—IMPACT (Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen)[2] and the POL (Preoperative Letrozole) trial[3]—tumor Ki67 2 to 4 weeks after initiating endocrine therapy, rather than at baseline, correlated with individual patient outcome.[2,4-6] We have therefore hypothesized that a 10% Ki67 early-in-treatment cut point can be used as an initial threshold for labeling a tumor endocrine-resistant.[1] At least 20% of ER-rich tumors are in this category and thus need more active systemic therapy than AI monotherapy. The Co-

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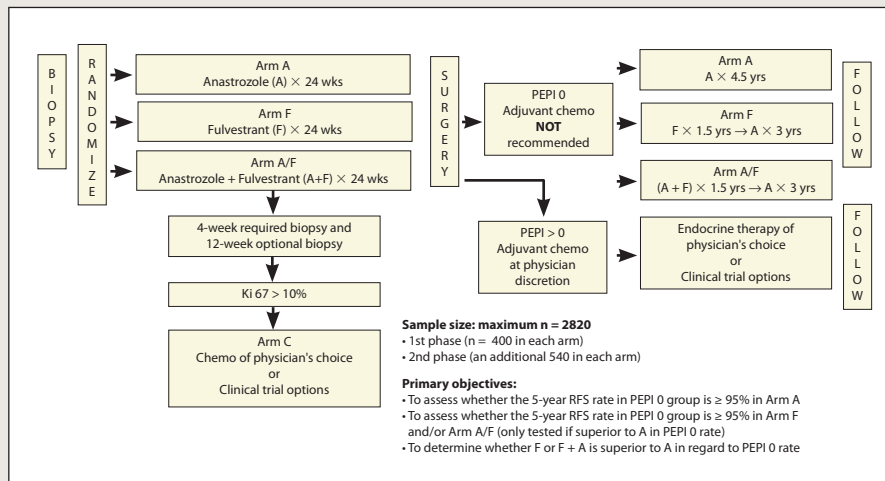


Figure: Study Schema for the Phase III ALTERNATE Trial—ALTERNATE=ALternate approaches for clinical stage II or III Estrogen Receptor positive breast cancer NeoAdjuvant TrEatment in postmenopausal women.

(ALTERNATE) to validate the use of PEPI 0 as a surrogate endpoint of endocrine therapy success (Figure). Tumor tissues are collected at baseline, at week 4 on therapy, and at the time of surgery. Biopsies at recur-

hort B of American College of Surgeons Oncology Group (ACOSOG) trial Z1031, a randomized phase II neoadjuvant comparison of the three AIs in postmenopausal women with ER-rich (defined by an ER Allred score of 6 to 8) clinical stage II or III breast cancer,[7] triaged patients with high Ki67 (> 10%) at 2 to 4 weeks on therapy to neoadjuvant chemotherapy, to assess pathologic complete response rate as a surrogate marker for chemotherapy sensitivity. The study has completed patient accrual; its results are eagerly awaited. Analyses of these resistant tumors are of great interest, and we urgently need to design trials based on therapeutic targets identified, among which the PI3 kinase pathway presents a rich source of options.[1,8]

The PEPI was developed through retrospective analysis of the P024 trial, correlating post neoadjuvant endocrine therapy tumor characteristics with long-term outcomes, and was subsequently validated in an independent data set from the IMPACT trial.[5] A PEPI score of 0 (T1/2, N0, Ki67 2.7% or less and ER positive), representing approximately 20% to 30% of ER-rich tumors, predicted the best outcome in the absence of chemotherapy, while the relapse rate was significantly higher in the PEPI non-0 group. The PEPI non-0 group provides another opportunity for early identification of endocrine resistance. Again, we come back to ACOSOG Z1031 to look for more answers in the tumor analyses, and a correlation with long-term outcome. As a successor trial to the ACOSOG Z1031, ACTION (the Alliance for Clinical Trials in Oncology) is launching a large neoadjuvant/adjuvant phase III study entitled “ALternate approaches for clinical stage II or III Estrogen Receptor positive breast cancer NeoAdjuvant TrEatment in postmenopausal women

reference as well as sub-studies of novel therapeutic agents in the endocrine-resistant groups (high Ki67 at 4 weeks or PEPI non-0 at surgery) are being planned. At the conclusion of this study, we hope to be in a better position to address ER-positive breast cancer based on a combination of assessment of neoadjuvant response to identify responders who only need endocrine monotherapy and targeted/personalized approaches to the patients with resistant disease. In light of variations in Ki67 analytical practice, the International Ki67 in Breast Cancer Working Group published comprehensive recommendations on the preanalytical and analytical assessment, interpretation, and scoring of Ki67 to facilitate the use of this important marker in clinical research and eventually clinical practice.[9]

How can we prevent the occurrence of secondary resistance? We have been content with the cytostatic effect of endocrine agents, but this treatment is clearly inadequate in many patients. It is time to develop more active treatments in the early-disease setting that actually eradicate ER-positive breast cancer before new mutations and secondary resistance have a chance to develop. In this regard, standard chemotherapy is not the answer.

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THE LIM/METZGER-FILHO/WINER ARTICLE REVIEWED: SHAHEENAH DAWOOD, ANA M. GONZALEZ-ANGULO

Hormone Receptor–Positive Breast Cancer: The Known and the Unknown

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Over the last decade, retrospective and prospective studies, as well as multiple editorials expressing various expert opinions, have been published that explore different aspects of the subtypes of breast cancer that we know to exist. Interestingly, with each piece of data and viewpoint published, we acknowledge the fact that breast cancer is a heterogeneous disease, comprising multiple subtypes about which there are myriad questions. The review by Lim and colleagues, on the natural history of hormone receptor–positive breast cancer, is timely as it gives us a comprehensive overview of the most important data on the subject published to date. It takes us through a proposed natural history of this disease derived from the existing data, and examines some of the interesting questions that have arisen.

What do we know about hormone receptor–positive disease? We know it has a known target for treatment with endocrine therapy; it is more chemotherapy-resistant compared with human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer; it tends to recur

late, possibly after completion of endocrine therapy; and like every other subtype identified, it, too, is heterogeneous. Yet has any of this knowledge changed the way we treat a woman with hormone receptor–positive cancer today, compared with a decade ago? The answer is probably both yes and no.

Consider a typical case of a postmenopausal woman with a T2N1M0 hormone receptor–positive HER2-negative breast cancer. The question that frequently arises is: Does this type of patient require chemotherapy? Berry et al[1] showed in a retrospective analysis of three prospective trials that the addition of chemotherapy resulted in an absolute improvement in 5-year disease-free survival of 22.8% and 7% in women with estrogen receptor–negative and estrogen receptor–positive disease, respectively. This indicates that a benefit exists, but not as much as that for women with hormone receptor–negative disease. How can we truly know the benefit of subjecting a patient to the potential toxicities of chemotherapy? The answer may come from genomic risk assessments of breast tumor tissues.

The recurrence score derived from Oncotype DX (Genomic Health, Inc) is able to categorize hormone receptor–positive, node-negative tumors into high and low risk groups that do and do not benefit from the addition of chemotherapy, respectively. Oncotype DX has been validated in multiple datasets, leading to its incorporation into practice guidelines. Its role in patients with node-positive disease is currently being investigated. Albain et al[2] used the recurrence score to determine the benefit of the addition of chemotherapy in patients with node-positive disease who were enrolled in the Southwest Oncology Group (SWOG) 8814 trial (which randomized women to endocrine therapy alone or to endocrine therapy and che-

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motherapy), demonstrating no benefit for the addition of chemotherapy in women with a recurrence score of less than 18 and a significant benefit in those with a recurrence score greater than or equal to 31. RxPONDER is a large prospective planned trial whose objective is to determine the benefit of chemotherapy among women with hormone receptor–positive breast cancer, one to three positive nodes, and a recurrence score less than or equal to 25. Thus, until the results are available, the standard would be to add chemotherapy to this patient's treatment regimen.

Despite having mechanisms in place to determine chemotherapy benefit in this cohort, unfortunately there is no precise way at present to determine the degree of benefit and resistance to endocrine therapy at the individual level of the patient with hormone receptor–positive breast cancer. Lim et al describe various mechanisms that could be potentially responsible for de novo and acquired endocrine resistance. The most studied of these mechanisms is the activated PI3 kinase pathway that confers resistance to endocrine therapy. One way to overcome this resistance is to combine endocrine therapy with an mTOR inhibitor such as everolimus (Afinitor), the benefit of which has been demonstrated in patients with hormone receptor–positive breast cancer who have progressed on endocrine therapy. Whether we can use this upfront in the adjuvant setting is a question that is being studied. Such agents are not without toxicity, however, and this warrants the development of methods that would allow up-front determination of specific tumors inherently resistant to endocrine therapy. Tumors that co-express HER2 are also known to be less responsive to endocrine therapy in the absence of an anti-HER2 agent, which raises the question of whether 1 year of adjuvant trastuzumab (Herceptin) is enough in women whose tumors co-express both receptors. The arm of the HERA (Herceptin Adjuvant) trial that is investigating 2 years of trastuzumab may shed some light on this issue. Another explanation for lack of response to endocrine therapy may simply be the inaccurate measurement of estrogen and progesterone receptor levels using immunohistochemistry, with studies indicating that the inaccuracy rate could be as high as 20%.^[3] Although the multitude of resistance mechanisms appears daunting, the ability to accurately determine up-front resistance to endocrine therapy is an active area of research. Recent and interesting work comes from Symmans et al,^[4] who developed the sensitivity to endocrine therapy (SET) index that assesses the expression of genes correlated with estrogen to better predict outcome in response to endocrine therapy.

The questions of how long to give adjuvant endocrine therapy, and how much of a role resistance mechanisms play in women with hormone receptor–positive breast cancer who recur upon completion of 5 years of adjuvant endocrine therapy are currently the focus of multiple clinical trials. Prospective studies have demonstrated the continued benefit of endocrine therapy, in postmenopausal women, in the form of an aromatase inhibitor following completion of 5 years of tamoxifen. Whether postmenopausal women who get up-front aromatase inhibitors will benefit from more than 5 years of endocrine therapy is a question currently under investigation. Such strategies are designed to reduce the late recurrence known to be associated with hormone receptor–positive disease. Accurately identifying women at risk for a late recurrence (who will specifically require continued suppression of the estrogen receptor pathway) will be important if we are to spare those who do not need it from the long-term effects of estrogen-deprivation therapy.

Three decades ago, data from prospective clinical trials revealed the benefit of endocrine therapy among women with hormone receptor–positive breast cancer. Three decades later, we have come a long way in understanding the biology of this disease and developing strategies to improve outcomes. No doubt molecular profiling will continue to play a crucial role in allowing individualization of treatment strategies. We still have a long way to go, however. The time ahead is an exciting one, with results of a number of clinical trials eagerly anticipated. Given the current rate of progress in this field, it may not be completely unlikely that women with hormone receptor–positive breast cancer will be cured of this disease in the foreseeable future.

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