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Adjuvant chemotherapy in luminal breast cancers

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SUMMARY

Luminal breast cancers are traditionally considered to comprise of tumors expressing estrogen receptor (ER) and represent the majority of breast cancers. These tumors are characterized by significant heterogeneity in phenotype, molecular signature, relapse patterns and therapeutic response to endocrine and chemotherapy. Whilst adjuvant endocrine therapy is standard of care in patients with tumors that express either ER and/or progesterone receptor (PR), the indication for adjuvant chemotherapy is less clear-cut. On average, ER-positive breast tumors derive less benefit from chemotherapy compared to ER-negative tumors, however there is still clearly a subset of patients with ER-positive tumors that are chemosensitive. The basis for the addition of chemotherapy to adjuvant endocrine therapy is usually guided by the clinician's estimation of prognosis and assessment of the endocrine sensitivity of the tumor. The use of chemotherapy in this setting, however, is highly variable. There is tremendous value in identifying subgroups of patients who can expect favorable outcomes with endocrine therapy and who may not require any additional therapy. Similarly, it is equally important, if not more important, to characterize patients with ER-positive disease who will derive a substantial benefit from cytotoxic chemotherapy. In this article, we aim to discuss the utility of current biomarkers used to guide decisions regarding chemotherapy in ER-positive, HER2-negative breast cancers.

Introduction

Luminal breast cancers are typically thought to comprise tumors expressing estrogen receptor (ER) and represent the majority of breast cancers. These are characterized by significant heterogeneity in phenotype, molecular signature, relapse patterns and therapeutic response to endocrine and chemotherapy. Progress in gene profiling techniques has confirmed biological heterogeneity at a molecular level with at least 2 intrinsic luminal subtypes identified (Luminal A and Luminal B) with distinct gene expression.[1,2] The two molecular luminal subtypes are comprised almost entirely of tumors expressing a variable degree of ER and/or progesterone receptor (PR). Luminal A tumors are characterized by estrogen regulated genes and better outcomes, and luminal B tumors are characterized by a higher genomic grade and poorer outcomes.[3,4] We will focus on ER-positive, HER2-negative breast tumors for the purposes of this review.

Whilst adjuvant endocrine therapy is standard of care in patients with tumors that express ER and/or PR, the indication for adjuvant chemotherapy is less clear-cut. It is well established that ER-positive breast tumors derive less benefit from chemotherapy compared to ER-negative tumors.[5] Whilst this may partly be explained by the routine use of endocrine treatments in ER-positive tumors, there is still clearly a subset of patients with ER-positive tumors that are chemosensitive. Data from a large meta-analysis of patients with ER-positive tumors from the Early Breast Cancer Trialist Collaborative Group (EBCTCG) reported a benefit with adjuvant chemoendocrine therapy over endocrine therapy alone with 5-year recurrence rate hazard ratios (HR) of 0.64 and 0.85 in patients aged less than and great than 50 years respectively.[6] The larger impact of chemotherapy in younger patients is likely to be partially explained by the endocrine effect of chemotherapy on ovarian function. It is may also be because a higher proportion of young women may have less endocrine sensitive cancers and more chemosensitive cancers than are seen in older women. Similar long-term disease-free survival (DFS) benefits with the addition of chemotherapy to adjuvant endocrine therapy are also noted in the phase III randomized NSABP B20 and SWOG 8814 trials.[7,8] In light of the morbidity and smaller absolute benefits of chemotherapy in ER-positive tumors, identifying predictors of chemosensitivity has been identified as a key challenge in better tailoring therapy to individuals with this breast cancer subset.

In the clinical setting, the basis for the addition of chemotherapy to adjuvant endocrine therapy is usually guided by the clinician's estimation of prognosis and assessment of the endocrine sensitivity of the tumor. Not surprising, the use of chemotherapy in clinical practice is highly variable. Prognostic determinants of breast cancer may be broadly divided into tumor burden (including both tumor size and nodal status) and tumor biology (such as tumor grade,

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ER, PR and HER2 expression, and indices of cell proliferation). The components of tumor biology are also used to guide the assessment of endocrine sensitivity of the tumor. A value of greater than 50% ER expression has been chosen by the St Gallen consensus panel to indicate highly endocrine responsive tumors.[9] The 2000 NIH clinical guidelines on adjuvant chemotherapy did not take into account tumor biology and recommended its use in tumors greater than 1 cm and in the presence of involved lymph nodes.[10] Nevertheless, since the relative benefits of chemotherapy in post-menopausal women is smaller than in pre-menopausal women in meta-analyses of early breast cancer trials,[6] some clinicians are more hesitant about administering chemotherapy to postmenopausal women, particularly those that are of more advanced age and/or have a limited tumor burden. Decisions based on demographic characteristics and tumor burden have the potential to over-treat many individuals and under-treat others. Robust biologic predictors of benefit are likely to be far more useful. In the end, the factors determining chemotherapy sensitivity are still poorly understood, and may not necessarily overlap entirely with negative predictors of endocrine sensitivity or prognostic determinants. For example, tumors that are endocrine sensitive may also be chemosensitive, whilst endocrine resistant and tumors with poor prognostic factors may not always be chemosensitive.

ER expression

It is well established that endocrine sensitivity is variable in luminal tumors and ER expression predicts for endocrine response. As accurate assessment of ER by immunohistochemistry (IHC) remains a challenge, an alternative approach to quantifying the degree of endocrine sensitivity is to measure the estrogen regulated genes as a more comprehensive measure of this critical signaling pathway. A set of 822 estrogen-induced genes was found to better predict long-term survival than the luminal A and B molecular signatures.[11] The utility of this estrogen-induced gene signature has not been prospectively used to determine chemosensitivity of luminal tumors. The assumption that chemosensitivity is inversely related to endocrine sensitivity is not clear cut. Evidence suggesting an inverse relationship between ER expression and chemotherapy benefit in luminal breast cancers was obtained from a study of post-menopausal women with ER-positive and lymph node-positive cancers from the International Breast Cancer Study Group (IBCSG) Trials VII and 12-93.[12] In this study, ER was measured by extraction assays in the majority of the tumor samples analyzed, although it has been demonstrated that there is high concordance between extraction assays and IHC and trial conclusions are the same regardless of the method used.[13] The addition of chemotherapy improved DFS in patients receiving chemotherapy (HR = 0.81, p = 0.02, median follow up 13 years), and non-parametric subpopulation treatment effect pattern plot (STEPP) analyses demonstrated that this benefit was limited to the patients whose tumors had low to intermediate levels of estrogen expression (<188 fmol/mg cytosol protein). A similar STEPP analysis of tumor ER and PR levels performed in the IBCSG Trial VII reported chemotherapy benefit in patients with tumors expressing intermediate ER and low levels of PR.[14] ER therefore has some overlapping role in predicting for good outcome, endocrine sensitivity and chemosensitivity, but these factors may not entirely overlap. It is likely however that there are other biological factors that interact with ER-signaling pathway to determine chemosensitivity.

Tumor grade

Histological tumor grade is a biomarker used traditionally for predicting poor prognosis, and is scored based on mitotic index, nuclear polymorphism and differentiation.[15] Besides being limited in reproducibility because of inter-observer variability, a high proportion of tumors are classified as intermediate grade, which represents a grey zone in aiding clinical decisions on chemotherapy in ER-positive tumors. A gene expression grade index (GGI) developed as a surrogate for histological grade, may be a better predictor of relapse-free survival (RFS).[16] Unlike histological grade, there is no intermediate grade category in the GGI, and the two subgroups identified were highly comparable to the luminal intrinsic subtypes, with luminal A tumors having low GGI scores and luminal B tumors with high scores. The GGI subgroups also correlate with risk groups using the 21-gene Oncotype recurrence score,[3] making it a more reliable biomarker of prognosis compared to histological grade. Although this confirms the central role of proliferation-related genes in predicting for prognosis in luminal tumors, prospective data on the utility of the GGI score to predict for chemotherapy benefit is however still lacking.

Cell proliferation indices

The percentage of proliferating cells in a tumor is an established predictor of breast cancer prognosis, and may be measured histologically using antibodies against the proliferation antigen Ki67.[17] Ki67 is not included in routine clinical decision-making because of inter-observer variability and uncertainty regarding how Ki67 values should influence clinical decisions. In luminal breast cancers, an IHC panel comprising ER, PR, HER2 and Ki67 (with a Ki67 index point of 13.25%) may be used to distinguish luminal A, luminal B and luminal-HER2-positive tumors according to outcomes, with the later two subtypes associated with poorer breast cancer recurrence-free and disease-specific survival in all adjuvant systemic treatment categories compared to luminal A tumors.[18] Whilst changes in Ki67 expression after neoadjuvant endocrine treatment may predict long-term outcome in ER-positive tumors,[19] there are mixed results with the utility of Ki67 as a predictive marker for chemosensitivity in the preoperative and adjuvant settings. In an analysis of 1521 premenopausal and postmenopausal patients with ER-positive tumors from the IBCSG VIII and IX trials respectively, a high Ki67 index was found to be associated with poorer DFS but did not predict for benefit with chemoendocrine therapy.[20] The chemotherapy used in these trials was cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), and did not include anthracyclines and taxanes. In contrast, a high Ki67 index was predictive of both outcome and benefit to adjuvant taxane chemotherapy in ER-positive breast cancers in subset analyses of the PACS01 and Breast Cancer International Research Group (BCIRG) 001 trials.[21,22] These were unplanned subset analyses and therefore these findings should only be considered hypothesis generating at this stage.

Multi-gene prognostic signatures

Perhaps the greatest advancement in biomarkers to determine chemosensitivity has been the development of multi-gene prognostic signatures derived from high-throughput analysis of tumor specimens for gene expression patterns, to identify subsets of patients with ER-positive breast cancers with improved outcomes following the addition of chemotherapy to endocrine therapy. Whilst a number of multi-gene signatures are able to identify subgroups of patients with varying risk of disease recurrence and death from breast cancer, only one assay has demonstrated utility in predicting for adjuvant chemotherapy benefit. Importantly, these assays also identify subsets of patients who do not benefit from chemotherapy and therefore may be spared its toxicity.

The 21-gene Oncotype Dx (Genomic Health, Redwood City, CA, USA) recurrence score (RS) is derived from a complex algorithm

calculated on the gene expressions of a pre-selected list of 16 genes of biological interest, including genes involved in estrogen signaling, cell proliferation, HER2 signaling, and five reference genes for normalization purposes.[23] The utility of the RS as a predictor of distant recurrence risk was first validated in patients with ER-positive and lymph node-negative samples obtained from the National Surgical Adjuvant Breast and Bowel (NSABP) trial B-14 in which patients were randomized to receive tamoxifen or placebo. Among the tamoxifen treated patients, the RS was shown to more accurately predict for distant recurrence than conventional clinicopathologic characteristics.[24] The utility of the RS to predict chemotherapy benefit was subsequently demonstrated in a retrospective analysis of NSABP B-20, a trial which randomized patients with node negative, ER-positive breast cancer to tamoxifen alone or tamoxifen plus chemotherapy. In this dataset, patients with a low RS did not benefit from chemotherapy, and those with a high recurrence score derived a dramatic benefit from chemotherapy.[23] Similar findings were also obtained from a retrospective analysis of the Southwest Oncology Group (SWOG) 8814 trial where post-menopausal patients with ER-positive, lymph node-positive disease were randomized to receive tamoxifen with and without anthracycline-based chemotherapy.[7] In both these studies, only the subgroup of patients with a RS score of greater than 31 had a clear benefit from the addition of chemotherapy. One of the primary advantages of the RS is that RNA may be extracted from archived formalin-fixed, paraffin-embedded tissue that is still the primary mode of preserving tissue histologically in most centers.

Another prognostic multi-gene signature that may have utility in predicting for adjuvant chemotherapy benefit is the FDA-approved 70-gene MammaPrint (Agendia, Amsterdam, Netherlands) signature. Unlike the 21-gene Oncotype RS where the genes were preselected, MammaPrint was developed using an unsupervised hierarchical clustering approach whereby the high risk gene signature predicted for poor outcomes in tumors of all subtypes.[25] This prognostic signature was subsequently validated in cohorts of patients with lymph node-negative breast cancer.[26] A retrospective analysis of pooled cohorts of patients with ER and/or PR-positive tumors demonstrated benefit in adding chemotherapy to endocrine therapy only in the subgroup of 70-gene high-risk patients.[27] While both the Oncotype and Mammoprint assays were tested retrospectively, the Oncotype RS was evaluated retrospectively in a prospectively assembled clinical trial. For this reason, there is far greater confidence, at this time, that the Oncotype assay can reliably predict which patients benefit from chemotherapy. In addition, unlike the 21-gene Oncotype platform, MammaPrint is performed on fresh-frozen tissue that may limit its routine use.

Both the 21 and 70 multi-gene signatures are currently undergoing prospective validation in large ongoing studies. The TAILORx trial will study the utility of the 21-gene RS signature to predict for chemotherapy benefit in the intermediate score range,[28] whilst the MINDACT trial will study the outcomes of patients with discordant risk assessments when using the 70-gene signature and clinicopathologic features using the Adjuvant! Online program (http://www.adjuvantonline.com).[29]

Preoperative endocrine prognostic index

Another strategy in identifying patients with luminal tumors who may require and potentially benefit from additional treatment options, including adjuvant chemotherapy, is to assess clinical and molecular response to preoperative endocrine therapy. A preoperative endocrine prognostic index (PEPI) for RFS and breast cancer specific survival (BCSS) based on the ER staining intensity, Ki67 index, tumor size and lymph node involvement of the tumor at surgery was developed from post-menopausal patients with ER-positive breast cancer in the PO24 preoperative trial which compared 4 months of letrozole to tamoxifen.[30] The PEPI score predicted for RFS in an independent study (IMPACT trial) that compared 3 months of preoperative anastrazole, tamoxifen or the combination of the two.[31] Despite the PEPI scores utility as an in vivo biomarker of prognosis and endocrine sensitivity, its utility as a predictor of chemosensitivity has still not been validated.

Conclusion

Current biomarkers used to guide decisions regarding adjuvant chemotherapy in ER-positive, HER2-negative breast cancers overlap to some extent but not completely with negative predictors of endocrine sensitivity and prognostic determinants. Prospective data on the utility on these biomarkers to predict chemosensitivity are limited and the most promising are likely not to be single biomarkers but multi-gene prognostic signatures that are better able to capture the multiple biological pathways that determine chemotherapy response.

In considering the benefits of adjuvant chemotherapy benefit in patients with ER-positive tumors, it is also important to consider the effect of therapy on relapse patterns. Patients with ER-positive tumors are at continued risk of relapse for many years after initial breast cancer diagnosis. More than half of all recurrences among women treated with adjuvant tamoxifen therapy occur between 6 to 15 years after diagnosis, and the benefit of the addition of chemotherapy in DFS was seen primarily in the first 5 years from diagnosis.[6] The limited benefit of chemotherapy in preventing late relapses is also reflected in the DFS patterns of patients with poor prognosis gene signatures with both the 21-gene RS and 70-gene MammaPrint assays.[23,32] Late recurrences and deaths remain a formidable clinical challenge in ER-positive breast cancer and chemotherapy is unlikely to be the answer to this problem.

The two fundamental challenges regarding adjuvant chemotherapy in ER-positive HER2-negative breast cancers are which patients should not receive chemotherapy and which patients should. Whilst there is tremendous benefit in identifying subgroups of patients with good outcomes with endocrine therapy who may not require any additional therapy, the challenge is to identify patients with poorer outcomes and the specific treatment strategies that would benefit them. In deciding which patient to recommend adjuvant chemotherapy, what ultimately matters is not the risk of recurrence but rather the likely benefit from the addition of chemotherapy.

Conflict of interest statement

E.P. Winer: Consultancy: Novartis; Research support: Genentech. E. Lim has no conflict of interest to declare.

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