A Practical Clinical Approach to Adjuvant Therapy in Breast Cancer—An Update

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Abstract

Adjuvant therapy for breast cancer has evolved to reflect the heterogeneous nature of the disease. Specific subtypes such as luminal, HER2-positive, and basal subtypes express different molecular markers that can be targeted by a variety of novel agents; therapy is tailored to the individual profile of each tumor. New risk-stratification models, including models based on a tumor's genetic expression, enhance assessments of recurrence risk so that the potential toxicities of a particular regimen can be weighed against the potential benefit. More precise tailoring of adjuvant therapy may be possible in the future with advances in pharmaco-genetics, which will help to predict an individual's response to various agents. Optimal adjuvant treatment of breast cancer involves tailoring therapy to the individual patient and tumor.

Keywords

Breast cancer, adjuvant therapy, HER2, estrogen receptor, chemotherapy, trastuzumab, aromatase inhibitors, tamoxifen

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Advances in gene expression and molecular profiling have clarified that breast cancer is not a single disease entity, but a heterogeneous disease with multiple subtypes. Breast cancers can now be categorized into the luminal subtypes, which express estrogen receptors (ERs), the human epidermal growth factor receptor 2 (HER2)-positive subtypes, which express *ERBB2*, and the basal subtypes, which tend to be negative for ERs and *ERBB2* expression;[1–3] each subtype is associated with a different prognosis. As a result, the adjuvant treatment of breast cancer has also evolved to reflect the heterogeneous nature of the disease. This evolution of treatment options illustrates the complexity of adjuvant therapy selection for patients with newly diagnosed breast cancer. This article will highlight the evolution of treatments and risk stratification models over time and introduce possible developments for the future of breast cancer therapy.

Selection of Adjuvant Therapy

The goals of systemic adjuvant therapy are to reduce the risk for recurrence and improve survival while causing minimal additional toxicity. The discovery of specific breast cancer subtypes that express different molecular markers has allowed the selection of breast cancer therapies to be tailored to the individual profile of a patient's tumor (including tumor size and lymph-node status), risk for recurrence, patient comorbidities, patient menopausal status, and patient desires.

Personalized Medicine in Breast Cancer in 2009

This individualized approach utilizes the presence of hormone receptors in breast cancer to provide specific anti-estrogen therapy, with or without systemic chemotherapy. The presence of HER2 over-expression is targeted by a chemotherapeutic regimen that includes trastuzumab. Patients with basal subtype breast cancers who lack specific targets for anti-estrogen or anti-HER2 therapy are candidates for chemotherapy only.

A subset of breast cancers exist that may be overtreated by systemic chemotherapy, and includes patients with node-negative, ER-positive disease. A 21-gene assay (Oncotype Dx) was developed to predict the risk for recurrence in this subset of patients.[4] Protein expression in 16 cancer-related genes and five reference genes were used to develop a recurrence score (RS) that would determine an individual cancer's risk for recurrence and predict overall survival (OS). Higher RS implied a greater risk for recurrence and, thus, a greater benefit from adjuvant chemotherapy. Those individuals with low RS would be expected to have a lower risk for recurrence and thus have limited benefit from adjuvant chemotherapy. The Program for the Assessment of Clinical Cancer Tests in Breast Cancer Patients with ER-Positive and/or Progesterone-Positive Axillary Node-Negative Candidate for Adjuvant Cytotoxic Therapy in Addition to Hormone Therapy (PACCT-1/TAILORx)

Table 1: Adjuvant Endocrine Therapy

Author	Year	Patient Population	Treatment	Number	DFS (%)	p-value	OS (%)	p-value
Fisher	2004	ER-positive, node-negative	Tam versus placebo, 15-years follow-up	2,892	13	<0.0001	6	0.0008
Fisher	2001	ER-positive, node-negative	Five years versus >five years of tam	1,172	5	0.03	3	0.07
ATAC trialists	2007	Post-menopausal, ER-positive	Ana versus tam, 100-month follow-up	5,216	4.1	0.003	0	0.7
Coates	2007	Post-menopausal, ER-positive	Let versus tam	4,922	3	0.007	0.7	0.35
Coombes	2007	Post-menopausal, ER-positive	Tam/exe versus five years of tam	4,724	3.3	0.0001	0.8	0.08
Goss	2005	Post-menopausal, ER-positive	Let versus placebo after five years of tam	5,187	4.6	<0.001	0.4	0.3

Tam = tamoxifen; ana = anastrozole; let = letrozole; exe = exemestan; ER = estrogen receptor; DFS = disease-free survival; ATAC = Arimidex, Tamoxifen, Alone or in Combination; OS = overall survival.

trial (n=10,500) is prospectively investigating the role of the OncotypeDX assay to assess which patients with early-stage breast cancer and an intermediate RS would be more likely to benefit from chemotherapy and to reduce the use of chemotherapy in those who are unlikely to benefit from it (NCT 00310180). A similar study, the Microarray in Node-Negative Disease May Avoid Chemotherapy (MINDACT) trial (n=6,000), is prospectively investigating the role of the 70-gene MammaPrint assay in order to assess the best individual therapy (endocrine therapy with or without chemotherapy) in patients with node-negative, ER-positive breast cancer. These two gene-expression profiling assays have outperformed standard clinicopathological risk assessment models in predicting risk for distant metastases and OS.[5,6]

Endocrine Therapy with Anti-estrogens

Tamoxifen

Among the first molecular markers targeted for individualized therapy were the ERs (see *Table 1*). The selective ER modulator tamoxifen was first evaluated in lymph-node-negative, ER-positive breast cancers in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, which randomized patients to tamoxifen 10mg twice daily or placebo.[7] Over four years of follow-up, there was a significant improvement in disease-free survival (DFS) among all subgroups of patients. This benefit persisted over 15 years of follow-up, with a documented improvement in recurrence-free survival (RFS) of 42% (13% absolute benefit) and OS of 20% (6% absolute benefit).[8] Although the optimal duration of treatment was initially unknown, patients treated with tamoxifen for more than five years experienced a lower DFS, RFS, and OS than those whose treatment was discontinued at five years.[9] The occurrence of tamoxifen resistance and clinically significant side effects such as thromboembolic disease, hot flashes, or uterine malignancy prompted a search for alternative agents in the adjuvant setting.

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Aromatase Inhibitors

Aromatase inhibitors, which prevent the peripheral formation of estrogen within adipose tissue and have been effective in post-menopausal women with advanced, hormone-receptor-positive, tamoxifen-resistant tumors,[10–13] are among the newer agents to be tested. The effect of anastrozole was compared with that of tamoxifen and the combination of both agents in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial of adjuvant hormonal therapy. Single-agent anastrozole was shown to be superior to tamoxifen alone in DFS, time to recurrence, and risk for contralateral breast cancer.[14] With 100 months of follow-up, anastrozole remained superior to tamoxifen in hormone-receptor-positive patients, with a relative improvement of 15% in DFS (4.1% absolute benefit), as well as improvements in the time to recurrence and the risk for contralateral breast cancer, but no appreciable difference in OS.[15] Similar results were reported in the Breast Intergroup (BIG) 1-98 trial of five years of adjuvant letrozole versus tamoxifen among post-menopausal women with receptor-positive early breast cancer, in which letrozole improved DFS by 18% (3% absolute benefit) compared with tamoxifen.[16]

The role of aromatase inhibitors given sequentially after tamoxifen was evaluated in the Intergroup Exemestane Study (IES) and the MA.17 study. Patients enrolled in the IES trial were randomized to switch to exemestane after two to three years of tamoxifen therapy or complete the original five years with tamoxifen. With five years of follow-up data, patients changing therapy to exemestane experienced an improvement in DFS by 24% (3.3% absolute benefit), with little change in OS.[17] The MA.17 trial randomized patients completing five years of adjuvant tamoxifen to five years of either letrozole or placebo.[18] The trial was stopped early when a pre-planned analysis found an improvement in DFS among those patients randomized to letrozole. OS was the same in both arms, but lymph-node-positive patients in the letrozole arm had statistically significantly better OS.

Taken together, these results suggest an improvement in outcomes, particularly DFS, among post-menopausal women with hormone-receptor-positive breast cancers assigned to take aromatase inhibitors rather than tamoxifen for adjuvant hormonal therapy or aromatase inhibitors following tamoxifen for extended adjuvant hormonal therapy. Although aromatase inhibitors reduce bone mineral density and increase fracture risk,[19,20] these risks are reduced by the concomitant use of bisphosphonates.[21] Consequently, the use of aromatase inhibitors in the adjuvant setting has become standard practice among post-menopausal women. Aromatase inhibitors are not indicated for

Table 2: Adjuvant Chemotherapy

Author	Year	Patient Population	Treatment	Number	DFS (%)	p-value	OS (%)	p-value
Fisher	1996	ER-negative, node-negative	M → F → leucovorin	731	15	<0.001	9/2	0.03/0.48*
Fisher	1996	ER-negative, node-negative	CMF	1,095	9	<0.001	3	0.06
Fisher	2004	ER-positive, node-negative	CMF + tam versus tam alone	1,577	10	<0.0001	4	0.063
Fisher	1990	Node-positive, ER-positive	AC + tam versus tam alone	1,124	17	0.0004	8	0.04
Fisher	1990	Node-positive, ER-negative	CMF x six months versus AC x two months	2,194	1	0.5	1	0.8
Levine	1998	Pre-menopausal, node-positive	CEF versus CMF	710	10	0.009	7	0.03
Henderson	2003	Node-positive	AC → P versus no P	3,121	5	0.0011	3	0.0098
Mamounas	2005	Node-positive	AC → P versus no P	3,060	4	0.007	0	0.46
Sparano	2008	Node-positive or high-risk node-negative	AC → P versus T (q1 or three weeks)	4,950	4.6§	0.006	3.2	0.01§
Jones	2006	Operable invasive disease	TC versus AC	1,016	6	0.018	4	0.045

*Tam = tamoxifen; A = doxorubicin; C = cyclophosphamide; M = methotrexate; F = fluorouracil; P = paclitaxel; T = docetaxel; E = epirubicin; ER = estrogen-receptor; DFS = disease-free survival; OS = overall survival. * For patients 50 years of age or older/younger than 50 years of age; § Results are for the weekly paclitaxel regimen compared with the q3 week regimen.*

pre-menopausal women, since the ovaries remain their major source of estrogen production. Tamoxifen, which remains a viable option for post-menopausal women, remains the only pharmacological choice for pre-menopausal women, although studies are under way (NCT 00066703, NCT 00066690) to assess the effect of ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists in these patients.[22,23] This includes a phase III trial designed to evaluate the role of ovarian function suppression and either tamoxifen or exemestane compared with tamoxifen alone as adjuvant therapy for pre-menopausal women with endocrine-responsive breast cancers (SOFT).

Chemotherapy

The role of adjuvant chemotherapy (see *Table 2*) for patients with node-negative breast cancer was first evaluated in the NSABP B-13 trial, which examined the effect of sequential methotrexate and fluorouracil (5FU) followed by leucovorin versus surgery alone in ER-negative breast cancer patients. After four years of follow-up, an improvement in DFS was noted,[24] an effect that persisted through eight years of follow-up, where DFS improved from 59 to 74% (p<0.001).[25] A similar effect was observed among ER-negative, node-negative patients assigned to post-operative chemotherapy with cyclophosphamide, methotrexate, and 5FU (CMF) versus surgery alone in the NSABP B-19 trial, where DFS improved from 73 to 82% (p<0.001) but OS improved only minimally.

The addition of CMF chemotherapy to tamoxifen in ER-positive, node-negative patients was documented in the B-20 trial, which randomized patients to CMF plus tamoxifen or tamoxifen alone. The addition of chemotherapy to hormone therapy improved the RFS by 48% (10% absolute benefit) and OS by 22% (4% absolute benefit) up to 12 years after treatment.[8] The effect of chemotherapy on tamoxifen-responsive breast cancer patients with node-positive disease was also confirmed in the B-16 trial, which documented an improvement in DFS from 67 to 84% (p=0.0004) in patients ≥50 years of age treated with doxorubicin + cyclophosphamide (AC) and tamoxifen versus tamoxifen alone, as well with improvements in distant DFS and OS.[26]

The relative efficacy of standard CMF chemotherapy, given initially over 12 months and subsequently over six months, was compared with the shorter two-month-long anthracycline-containing regimen of AC chemotherapy in the B-15 protocol, which randomized patients with node-positive disease unresponsive to tamoxifen. The 63-day AC protocol was as effective as the 154-day CMF protocol in DFS and OS, with the CMF-treated patients requiring more office visits, anti-nausea therapy, and experiencing similar degrees of alopecia. Therefore, the AC regimen was considered preferable due to a shorter duration of therapy, similar toxicities, and a similar degree of benefit.[27]

Several other studies have examined the role of various anthracycline-containing regimens compared with standard CMF; all showed no significant differences in DFS or OS.[28–30] However, a phase II study of intensive cyclophosphamide, epirubicin, and 5FU (CEF) versus CMF for six months documented an improvement in DFS from 53 to 63% (p=0.009) and OS from 70 to 77% (p=0.03), although CEF was associated with a higher rate of febrile neutropenia and acute leukemia.[31]

The addition of a taxane to chemotherapy regimens was first investigated by the addition of paclitaxel for four cycles following four cycles of AC chemotherapy (with three doxorubicin dose escalation arms of 60, 75, and 90mg/m^2) in women with node-positive disease in the Cancer and Leukemia Group B (CALGB) 9344 trial. Although the escalation of the dose of doxorubicin did not affect outcomes, the addition of paclitaxel improved DFS (65–70%) and OS (77–80%) at five years, with minimal additional toxicity. The benefit of paclitaxel was most significant for those patients with ER-negative tumors rather than ER-positive tumors (most of whom were also treated with tamoxifen).[32] In 2005, the NSABP B-28 trial reported similar findings, with the addition of paclitaxel after four cycles of AC improving DFS by 4% (absolute benefit) with a small but non-significant improvement in OS.[33] The optimal taxane choice and dosing regimen was examined in a trial of paclitaxel or docetaxel every one or three weeks following standard AC chemotherapy. Compared with standard paclitaxel every three weeks, weekly paclitaxel was the most effective at improving DFS (76.9–81.5%) and OS (86.5–89.7%) at five years, although this regimen was also more likely to cause grade 2–4 neuropathy.[34]

The role of taxanes in adjuvant chemotherapy has expanded after the US Oncology (USO) trial USO9735 examined the role of four cycles of docetaxel and cyclophosphamide (TC) in early-stage invasive breast

Table 3: Adjuvant Human Epidermal Growth Factor Receptor-2-positive Therapy

Author	Year	Patient Population	Treatment	Number	DFS (%)	p-value	OS (%)	p-value
Romond	2005	HER2-positive	AC → P/H versus P alone	3,676	18.2	<0.0001	4.8	0.015
Smith	2007	HER2-positive, node-positive or high-risk node-negative	Standard chemotherapy or neoadjuvant chemotherapy → H or no H	3,401	6.3	<0.0001	2.7	0.0115
Slamon	2007	HER2-positive	AC → T versus AC → T/H versus TC/H	3,222	39/33	<0.0001/ 0.0003	41/34	0.0041/ 0.017*
Joensuu	2006	HER2-positive, node-positive or high-risk node-negative	T or V → CEF→ H or no H	232	11	0.01	6	0.07

** Relative risk reductions compared with doxorubicin, cyclophosphamide → docetaxel. A = doxorubicin; C = cyclophosphamide; P = paclitaxel; T = docetaxel; H = trastuzumab; E = epirubicin; C' = carboplatin, V= vinorelbine; F = fluorouracil; DFS = disease-free survival; OS = overall survival.*

cancer (zero to three positive lymph nodes) compared with four cycles of standard AC.[35] This trial demonstrated that at five years the non-anthracycline-containing regimen was associated with a DFS rate that was significantly superior for TC compared with AC (86 versus 80%, respectively, hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.50–0.94; p=0.015). The initially reported OS rates for TC and AC were 90 and 87%, respectively (HR 0.76, 95% CI 0.52–1.1; p=0.13). These differences persisted at 6.9 years of follow-up, with DFS improving from 79 to 85% (p=0.018) and OS improving from 84 to 88% (p=0.045) with the use of TC.[36]

Human Epidermal Growth Factor Receptor-2-positive Disease

HER2-positive breast cancers overexpress the HER2 transmembrane growth factor receptor and are associated with a generally poor prognosis.[37,38] In 1998, trastuzumab, a monoclonal antibody designed to target the extracellular domain of this protein, was approved as first-line therapy of metastatic HER2-positive breast cancer in conjunction with paclitaxel. Based on this approach, two large randomized trials were developed in the US to examine the effect of this agent in the adjuvant setting (see *Table 3*). The NSABP B-31 trial and the North Central Cancer Treatment Group (NCCTG) N9831 trials were both designed to test the effects of trastuzumab when added to a standard regimen of AC chemotherapy followed by paclitaxel in patients with HER2-positive disease. Patients were randomized to complete the standard chemotherapy approach with or without the addition of trastuzumab for one year. When the results of these studies were combined, the addition of trastuzumab reduced the risk for recurrence by 52% and improved DFS by 18.2% (absolute benefit) at four years. The relative risk for death also decreased by 33% (4.8% absolute benefit) with the addition of trastuzumab.[39] However, the use of adjuvant trastuzumab was also associated with a small (0.4–3.8%) but significant risk for congestive heart failure.[40,41]

The success of specifically targeted therapy with trastuzumab has introduced a new age in breast cancer treatment, with novel agents targeting the underlying molecular processes in malignancy.

Similar results have been observed in a variety of other studies. This included the two-year follow-up data of trastuzumab following standard adjuvant or neo-adjuvant chemotherapy in the European Herceptin Adjuvant (HERA) trial,[42] which reported that one year of trastuzumab improved the risk for disease recurrence by 36% (6.3% absolute benefit; p<0.0001) and reduced the risk for death by 34% (2.7% absolute benefit; p=0.0115). Similarly, the Breast Cancer International Research Group (BCIRG)-006 trial demonstrated that trastuzumab significantly improves DFS and OS among patients with node-positive or high-risk node-negative disease treated with AC followed by docetaxel or a non-anthracycline regimen of docetaxel plus carboplatin compared with the standard chemotherapy approach of AC followed by docetaxel.[43] The Finnish Fin-Her trial also demonstrated that the addition of even a short nine-week treatment with trastuzumab to node-positive or high-risk, node-negative patients completing chemotherapy with docetaxel or vinorelbine followed by 5FU, epirubicin, and cyclophosphamide (FEC) reduced the risk for recurrence (HR 0.42, 95% CI 0.21–0.83; p=0.01).[44] These studies confirm the advantage of using trastuzumab in conjunction with adjuvant chemotherapy in high-risk HER2-positive patients.

Future Directions

The success of specifically targeted therapy with trastuzumab has introduced a new age in breast cancer treatment, with novel agents targeting the underlying molecular processes in malignancy. Lapatinib is a dual tyrosine kinase inhibitor—it inhibits both HER1 and HER2 tyrosine kinase activity—that was approved in 2007 for use with capecitabine in patients with HER2-positive locally advanced or metastatic breast cancer progressing on standard therapies such as anthracyclines, taxanes, and trastuzumab.[45] Its use is currently being investigated in the adjuvant setting in the international Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation trial (ALTTO), which will determine the optimal combination/sequence of lapatinib and trastuzumab (lapatinib alone versus trastuzumab alone versus trastuzumab followed by lapatinib versus trastuzumab concurrently with lapatinib) in newly diagnosed HER2-positive patients (NCT 00490139).

Bevacizumab, a monoclonal antibody designed to inhibit the vascular endothelial growth factor (VEGF), which is necessary for tumor angiogenesis, has been found to be beneficial in several solid tumors, including metastatic breast cancer,[46] and is currently being evaluated in several trials in the adjuvant breast cancer setting. These trials include the Eastern Co-operative Oncology Group (ECOG)-5103

trial (a phase III study of AC chemotherapy followed by paclitaxel with or without bevacizumab in node-positive or high-risk node-negative disease, NCT00433511), the BEATRICE study (a European two-arm open-label study that will evaluate the efficacy and safety of the addition of bevacizumab to standard adjuvant therapy in 2,530 patients with 'triple- negative' breast cancer), and the Bevacizumab and Trastuzumab Adjuvant Therapy (BETH) trial (a phase III trial developed by the NSABP Foundation and the BCIRG that will recruit approximately 3,500 patients with HER2 + breast cancer). Bevacizumab is also being investigated with other agents in other settings, including inflammatory breast cancer, neo-adjuvant chemotherapy for locally advanced breast cancer, or metastatic disease.

As novel agents are found to have efficacy in advanced breast cancer, many will be tested in the adjuvant setting, and many non-chemotherapy agents are currently under investigation. These include bisphosphonates such as zoledronic acid, clodronate, or ibandronate (the S307 trial, NCT00127205). There is renewed interest in testing such agents as adjuvant therapy following the recent finding that pre-menopausal patients treated with zoledronic acid experienced an improvement in DFS when this drug was added to adjuvant endocrine therapy.[47]

Future adjuvant therapy studies may also include receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors, other HER-2 tyrosine kinase receptor inhibitors, epidermal growth factor receptor inhibitors, c-kit growth factor receptor inhibitors, and Src tyrosine kinase inhibitors, which are currently being studied in a variety of locally advanced or metastatic breast-cancer protocols.

Lastly, the concept of personalized therapy is being advanced by the understanding that pharmacogenetics (PGs) play an important role in the efficacy of any therapy. Emerging data show that patients respond differently to tamoxifen depending on the PG make-up.[48] In the future, more precise tailoring of adjuvant therapy may be possible based on a PG profile.

Conclusion

The goals of adjuvant therapy in breast cancer are to reduce the risk for recurrence and improve survival with the least acute and/or chronic toxicity possible. The availability of robust risk-stratification models, including models based on tumor genetic profiles, allows a precise assessment of recurrence risk so that the potential toxicity of planned adjuvant therapy can be weighed against the expected benefit. The treatment of choice for adjuvant breast cancer therapy will also continue to evolve as newer agents become available.

Limited hormonal and chemotherapeutic options were available in the past and resulted in potentially severe, unwanted side effects. The selection of treatment options has expanded in recent years since the development of trastuzumab, the first monoclonal antibody approved for targeted therapy in breast cancer. Currently, several other immunomodulators and tyrosine kinase inhibitors are being explored. These agents, in combination with standard chemotherapy, may continue to reduce the risk for recurrent disease and improve survival. Treatment has become an individualized process that requires tailoring the medication selection to the specific characteristics of a patient's cancer, so that there is no longer a one-size-fits-all approach to this disease. ■

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