Adjuvant Chemotherapy for Early-stage Breast Cancer

a report by

Heather L McArthur, MD, FRCPC[1] *and* **Clifford A Hudis, MD**[2]

1. Clinical Research Fellow, Breast Cancer Medicine Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York; 2. Chief, Breast Cancer Medicine Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, and Professor of Medicine, Weill Medical College, Cornell University, New York

DOI: 10.17925/OHR.2007.00.2.57

A highly publicized study delineating the trend in incident breast cancer diagnoses in the US was recently reported.[1,2] In this study, a sharp decline in age-adjusted incident breast cancer cases was observed among American women in 2003 compared with 2002. Furthermore, an 8.6% decline in age-adjusted annual incidence rates was observed between 2001 and 2004. This decline was evident only for women 50 years of age or older, and was more pronounced for women with estrogen-receptor positive (ER+) breast cancer compared with those with ER-negative disease.

This decrease in incident breast cancer diagnoses appeared related to the early reports of the Women's Health Initiative (WHI), which described the deleterious effects of hormone replacement therapy (HRT), including increased risk of coronary artery disease and incident breast cancers.[3] Subsequently, HRT prescriptions declined by 38% in the US by the end of 2002, and it is believed that this decline accounted for the observed improvements in breast cancer incidence rates.[4] However, despite this progress, breast cancer remains a significant public health burden with more than 200,000 new cases diagnosed in the US each year,[5] and more than 1 million cases diagnosed worldwide each year.[6]

Although an increasing proportion of these new breast cancer diagnoses represent potentially curable early-stage disease, a significant proportion of women with early-stage disease will ultimately experience a distant relapse and die of breast-cancer-related complications. Consequently, efforts to identify innovations in the adjuvant treatment strategy and, thus, optimize outcomes for women with early-stage breast cancer are ongoing. Recently, a number of therapeutic innovations have been reported, most notably in adjuvant taxane-containing and dose-dense strategies. Insights into the response of HER2-positive breast cancers to specific therapies have also been reported. Selected innovations and insights will be reviewed here.

Advances in Adjuvant Chemotherapy

The optimal chemotherapy strategy for women with early-stage breast cancer has not yet been determined. The ideal paradigm would permit clinicians to identify specific subgroups of women who derive significant benefit from specific treatment strategies, and spare subgroups of women who do not derive benefit from the potentially deleterious effects of treatment. However, this tailored approach to adjuvant treatment recommendations often proves clinically challenging. For example, although the development of taxane-containing regimens represented a milestone in therapeutic innovation with significant benefits demonstrated in multiple adequately powered randomized trials, taxanes are also associated with considerable rates of clinically significant toxicity. Distinguishing subgroups of women who derive benefit from taxane-containing strategies from those who do not remains clinically challenging. Consequently, investigators strive to further characterize the risk–benefit calculus for subgroups of women with early-stage breast cancer, so that recommendations for taxane-containing strategies may be reserved for the populations likely to derive the greatest benefit.

Taxane-containing Chemotherapy Strategies

Efficacy of Adjuvant Taxane-containing Regimens

A number of adequately powered randomized trials have now reported improved outcomes for early-stage breast cancer patients treated with either adjuvant paclitaxel or docetaxel. Recently, the overall efficacy of adjuvant taxane-containing strategies was confirmed in both pooled and meta-analyses.[7,8] In the pooled analysis, outcomes for 15,598 patients participating in nine adjuvant taxane trials were evaluated.[7] Significant disease-free survival (DFS) benefits were reported both overall (relative risk (RR) 0.86; p=0.00001) and in the lymph-node-positive subset (RR 0.84; p=0.0001). Survival benefits were also reported both overall (RR 0.87; p=0.0001) and in the lymph-node-positive subset (RR 0.84; p=0.0001). The absolute DFS and overall survival (OS) benefits ranged from 3.3 to 4.6% and from 2 to 2.8%, respectively, in favor of the taxane-containing strategies. Similar improvements were reported in the meta-analysis of 18,304 women participating in 12 adjuvant taxane studies.[8] In this study, the hazard ratio (HR) for survival was 0.81 (p<0.00001) in favor

Heather L McArthur, MD, FRCPC, is a Breast Cancer Medicine Clinical Research Fellow at the Memorial Sloan-Kettering Cancer Center, New York. She has received a number of merit awards in recognition of her research, including a Research and Development Fellowship awarded by the Canadian Institute for Health Research (CIHR) and the Canadian Association of Medical Oncologists (CAMO) and a 2007 American Society of Clinical Oncology (ASCO) Foundation Merit Award. Dr McArthur completed her fellowship in medical oncology at the British Columbia Cancer Agency in Vancouver.

E: mcarthuh@mskcc.org

Clifford A Hudis, MD, is Chief of the Breast Cancer Medicine Service and Attending Physician at Memorial Sloan-Kettering Cancer Center (MSKCC), New York. He is also a Professor of Medicine at the Weill Medical College of Cornell University, New York. Dr Hudis is Chair of the Scientific Advisory Board of the Breast Cancer Research Foundation (BCRF), Chair of the Information Technology Committee of the American Society of Clinical Oncology (ASCO), Co-Leader of the Breast Disease Management Team at MSKCC, and Co-Chair of the Breast Committee of the Cancer and Leukemia Group B (CALGB).

E: hudisc@mskcc.org

of the taxane-containing strategies. Thus, both studies confirmed significant survival benefits with the incorporation of taxanes into the adjuvant strategy. However, whether specific subgroups, particularly women with node-negative disease, derive benefit from adjuvant taxane-containing strategies remains uncertain. It is hoped that a forthcoming meta-analysis on this topic by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) will provide further insights.

Given the observed clinical benefits demonstrated with adjuvant taxane-containing strategies, investigators strive to further refine these strategies by evaluating the impact of dose and scheduling.

Evaluation of Taxane Formulations

Given the observed clinical benefits demonstrated with adjuvant taxane-containing strategies, investigators strive to further refine these strategies by evaluating the impact of dose and scheduling. For example, in the Eastern Cooperative Oncology Group (ECOG) 1199 trial, weekly versus q3 weekly schedules of paclitaxel or docetaxel after four cycles of q3 weekly adriamcycin/cyclophosphamide (AC) were evaluated.[9,10] The results of this study were originally reported in 2005 with a trend toward a DFS benefit with weekly paclitaxel administration.[9] However, at the time of the updated analysis in 2007, after a median 63.8 month follow-up period and 1,048 recorded DFS events, no difference was observed with either taxane or taxane schedule.[10] However, significant increases in toxicity rates were observed with docetaxel compared with paclitaxel. In an exploratory subset analysis, benefits were observed with weekly paclitaxel in the hormone-receptor-negative population and with the q3 weekly docetaxel regimen in the hormone receptor-positive population. However, although provocative and hypothesis-generating, exploratory analyses must be interpreted with caution.

Evaluation of Taxane Schedules

Many adjuvant chemotherapy regimens comprise both a taxane and an anthracycline. Conventionally, the anthracycline is administered prior to the taxane when sequential therapy is planned. Recently, this sequencing convention was challenged in a randomized phase II study of four cycles of dose-dense (q2 weekly) docetaxel (75mg/m^2) before or after four cycles of dose-dense conventional dose AC (60/600mg/m^2).[11] The relative dose intensity (RDI) proved superior with up-front docetaxel administration, primarily as a consequence of the decrease in associated dose reductions with this strategy. However, whether this increase in RDI will translate into improvements in clinical outcomes has not yet been determined.

Another adjuvant scheduling convention under investigation is sequential versus concurrent anthracycline–taxane administration. For example, in an exploratory analysis from a phase III study of 617 women with node-positive operable breast cancer who were randomized to epirubicin (E) administered either sequentially or concurrently with either paclitaxel or docetaxel, no significant DFS difference was observed between the study arms.[12] Furthermore, consistent with ECOG 1199, there was no superiority of one specific taxane.

In Breast International Group (BIG) 2-98, 2,887 women with node-positive breast cancer were randomized to one of four adjuvant chemotherapy arms: doxorubicin (A) (75 mg/m^2) for four cycles followed by four cycles of oral cyclophosphamide (100mg/m^2 on days one to 14), methotrexate (40mg/m^2 on days one and eight), and 5-fluorouracil (600 mg/m^2) (poCMF); four cycles of AC followed by three cycles of conventionally dosed IV cyclophosphamide, methtrexate, and 5-fluorouracil (CMF); three cycles of A (75mg/m^2) followed by three cycles of docetaxel (100mg/m^2) followed by three cycles of CMF; or four cycles of A (50mg/m^2) followed by four cycles of docetaxel (75mg/m^2) followed by four cycles of CMF.[13] At the time of the initial report, the sequential A–docetaxel arm proved superior to the A and concurrent A–docetaxel arms for DFS. However, survival was not superior for any of the evaluated regimens. In a subsequently reported central nervous system (CNS) substudy, the incidence of brain metastases detected *post mortem* was evaluated.[14] In this substudy, although the taxane-containing strategies were associated with higher rates of abnormal cerebrospinal fluid (CSF) cytology (11.9 versus 3.1%) and magnetic resonance imaging (MRI) studies, no difference was observed in CNS relapse rates between the taxane and non-taxane cohorts.

Estrogen Receptor Expression and Taxane Efficacy

In the ideal adjuvant treatment paradigm, women who derive benefit from specific regimens would be identified while those who do not would be spared the deleterious effects of treatment. To this end, the potential relationship between ER expression and taxane efficacy was recently explored in a pooled analysis of 3,490 patients participating in two international research studies: the Breast Cancer International Research Group (BCIRG) 001 and the French Adjuvant Study group (PACS) 01.[15] In BCIRG 001, six cycles of adjuvant docetaxel, adriamycin, and cyclophosphamide (TAC) were compared with six cycles of concurrent 5-fluourouracil, adriamycin, and cyclophosphamide (FAC), with five-year DFS

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(75 versus 68%; p=0.001) and OS (87 versus 81%; p=0.008) benefits reported with the taxane-containing strategy.[16] In PACS 01, six cycles of adjuvant 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) were compared with three cycles of FEC followed by three cycles of docetaxel (FEC–D).[17] In the recent analysis of pooled data from the two studies, DFS and OS benefits were reported for both the ER-positive and ER-negative cohorts, although there was no significant difference in the test for interaction between ER status and chemotherapy regimen. However, given the predictive capacity of ER positivity for response to anthracycline-containing regimens,[18] the relationship between ER status and response to taxanes was also explored. In this analysis, the relative efficacy of docetaxel did not differ significantly for patients with strongly ER-positive tumors compared with those with weak or intermediately ER-positive tumors. However, the confounding effects of dose size, number of taxane cycles administered, and differences in specific regimens administered limit the

Table 1: Working Group on Gynecology and Oncology (AGO) Study Schema

Regimen	Schedule	Total Cycles/Drug	Epirubicin		Paclitaxel		Cyclophosphamide	
			Per Cycle	Total	Per Cycle	Total	Per Cycle	Total
ETC	Twice weekly	3	150mg/m^2	450mg/m^2	225mg/m^2	675mg/m^2	2,500mg/m^2	7,500mg/m^2
EC–T	Thrice weekly	4	90mg/m^2	360mg/m^2	175mg/m^2	700mg/m^2	600mg/m^2	2,400mg/m^2

ETC = sequential epirubicin, paclitaxel, and cyclophosphamide; EC–T = epirubicin/cyclophophamide followed by paclitaxel.

Table 2: National Cancer Institute of Canada (NCIC) MA.21 Schema

Regimen	Schedule	Total Cycles	Anthracycline		Taxane	Cyclophosphamide	5FU
			Per Cycle	Total			
CEF	Thrice weekly	6	60mg/m^2 IV D1 and D8	720mg	N/A	75mg/m^2 po D1–14	500mg/m^2 D1 and D8
AC–T	Thrice weekly	8	60mg/m^2 IV D1	240mg	175mg/m^2 IV D1	600mg/m^2 IV D1	N/A
EC–T	Twice weekly	10	120mg/m^2 IV D1	720mg	175mg/m^2 IV D1	830mg/m^2 IV D1	N/A

5FU = 5-fluorouracil; CEF = oral cyclophosphamide, epirubicin, and 5-fluorouracil; AC–T = adriamycin, cyclophosphamide, and paclitaxel; EC–T = epirubicin, cyclophosphamide, and paclitaxel; D = day; po = by mouth.

interpretation of this analysis. It seems certain that a global taxane–hormone receptor interaction is unlikely to be absolute.

Dose Density

The aim of the dose-dense strategy is to sequentially eradicate the numerically dominant, rapidly proliferating cell populations and then eradicate more indolent resistant cells, thereby optimizing tumor cell kill.[19,20] This strategy was first evaluated in the adjuvant setting in Cancer and Leukemia Group B (CALGB) 9741, a large randomized trial of dose-dense AC–paclitaxel (T).[21,22] Given the survival benefits demonstrated in CALGB 9741, the dose-dense strategy has since been evaluated in a number of other settings. For example, in a recently reported study 1,284 women with 'high-risk' node-positive early-stage breast cancer were randomized to a sequential course of three cycles of E, T, and C (150/225/2,500mg/m^2) for a total of nine cycles administered every two weeks with granulocyte colony-stimulating factor (G-CSF) support, or four cycles of q3 weekly EC (90/600mg/m^2) followed by four cycles of q3 weekly T at 175mg/m^2.[23] Of note, this study schema introduced not only dose density but also dose intensity (see *Table 1*). After a median 62-month follow-up period, the most impressive survival benefits to date in this high-risk population were reported. Specifically, OS was 82 versus 77% in the experimental and control arms, respectively (p=0.029). Although the applicability of these results is somewhat limited by the introduction of both dose density and dose intensity, we can envisage the study as delivering the same functional doses of the three drugs given the existing evidence for a limited dose–response relationship for all three active components. Consequently, one may infer that the dose-dense schedule more than compensated for the difference in dose intensity between the two study arms.

Recently, National Cancer Institute of Canada (NCIC) MA.21 also explored the impact of dose density. In this study, women aged 60 years or younger with node-positive or 'high-risk' node-negative breast cancer were stratified by nodal status, ER status, and primary surgery, and randomized to six cycles of q3 weekly oral cyclophosphamide, epirubicin, and 5-fluorouracil (CEF), four cycles of q3 weekly adriamycin and cyclophosphamide followed by four cycles of q3 weekly paclitaxel (AC–T), or six cycles of q2 weekly epirubicin and cyclophosphamide followed by four cycles of q2 weekly paclitaxel (EC–T) (see *Table 2*).[24] At the recently reported interim analysis, the adjusted three-year RFS was 90.1, 89.5, and 85%, for the CEF, EC–T, and AC–T regimens, respectively. In an exploratory analysis, there was a non-significant trend toward superiority of EC–T compared with CEF in the ER-negative subgroup (HR 0.78; p=0.23). Furthermore, q3 weekly AC–T proved inferior to both CEF and dose-dense EC–T in the same exploratory analysis (hazard ratio (HR) 1.67, p=0.007; HR 2.15, p=0.0002, respectively). However, CEF and EC–T were associated with increased rates of febrile neutropenia, thromboembolic events, and delayed cardiotoxicity compared with AC–T. Therefore, these results are consistent with other adequately powered randomized studies in support of the dose-dense strategy. The NCIC MA.21 investigators also concluded that given the inferiority of AC–T compared with CEF, and the equivalence of CEF with dose-dense EC–T, that taxanes may not be necessary in selected patients. It is anticipated that the forthcoming meta-analysis by the EBCTCG will provide further insights into the topic.

> Whether this enhanced sensitivity of HER2-positive breast cancers to anthracyclines is a function of HER2 and topoisomerase IIα co-amplification is uncertain.

Advances in Targeted Therapy with Trastuzumab

A number of the pivotal adjuvant trastuzumab (Herceptin®) trials were recently updated.[25–30] For example, in the Herceptin Adjuvant (HERA) study, women with node-positive or high-risk node-negative HER2-positive breast cancer were randomized to observation, one year of trastuzumab, or two years of trastuzumab after their primary chemotherapy.[25] The benefits of one year of trastuzumab versus observation were initially reported in 2005, with significant two-year DFS benefits (85.8 versus 77.4%, respectively; p<0.0001). In a recently updated analysis after a median two-year follow-up period, OS benefits were also reported (HR 0.66; p=0.0115).[26] Efficacy results from the two-year trastuzumab arm have not yet been reported.

Recently, the results of the joint analysis of National Surgical Adjuvant Breast and Bowel Project (NSABP) B31 and N9831 were also updated.[27,28] In these studies, trastuzumab was administered concurrently with chemotherapy

and then as monotherapy for a total of one year of trastuzumab therapy. In the updated analysis, the DFS and OS benefits originally reported in 2005 proved sustained after a median follow-up period of 2.9 years.

In BCIRG 006, patients with node-positive or 'high-risk' node-negative HER2-positive breast cancer were randomized to one of three study arms: four cycles of AC followed by four cycles of docetaxel (AC–D); AC–D with trastuzumab initiated concurrently with D and administered for a total duration of one year (AC–DH); or six cycles of docetaxel/carboplatin with trastuzumab administered concurrently and then as monotherapy for a total duration of one year (DCH).[29,30] At the time of the first planned interim analysis in 2005, an HR of 0.49 ($p<0.0001$) for AC–DH and an HR of 0.61 for DCH ($p<0.0002$) compared with the control arm were reported. A second interim analysis was recently reported with sustained DFS benefits for both trastuzumab-containing arms compared with the control arm (HR 0.61 and 0.67, respectively).[30] Although the magnitude of these DFS benefits were diminished compared with the first analysis, a small but significant OS benefit was now observed with the trastuzumab-containing regimens.

> Typically, hormone therapy alone is recommended for women with low-risk scores, while both hormone therapy and chemotherapy are recommended for women with high-risk scores.

HER2 Expression and Chemosensitivity

Identification of subsets of women who derive benefit from specific chemotherapy regimens remains an ongoing area of investigation. For example, the BCIRG 006 investigators reported the results of an exploratory analysis of the predictive capacity of HER2 and topoisomerase IIα gene co-amplification.[29,30] Specifically, women with breast cancers exhibiting co-amplification of both HER2 and topoisomerase IIα (the DNA replication and recombination enzyme targeted by anthracyclines) appeared to derive a therapeutic advantage with anthracycline–trastuzumab therapy, while women without the co-amplification did not. The implication was that there may be a population of women with HER2-positive breast cancer who may forgo anthracycline-based regimens and the associated risk of cardiotoxicity.

In a recent pooled analysis on the interaction between the predictive capacity of HER2 on responsiveness to adjuvant chemotherapy, the subset analyses from seven randomized controlled trials were analyzed.[31] Investigators reported a 29% reduction in the risk of relapse and a 27% reduction in the risk of death among adjuvant trastuzumab-naïve, anthracycline-treated women with HER2-overexpressing breast cancer compared with the non-overexpressing cohort. Therefore, the authors concluded that the superiority of anthracycline-based adjuvant chemotherapy appears to be limited to the HER2-positive cohort. Whether this enhanced sensitivity of HER2-positive breast cancers to anthracyclines is a function of HER2 and topoisomerase IIα co-amplification is uncertain. However, it is important to note that these data were collected in the pre-trastuzumab era. Thus, the significance of these findings in the modern era, in which trastuzumab is administered routinely, remains uncertain.

Table 3: HER2 Testing and Relative Risk in a Study of Adjuvant Trastuzumab

Category	Number ACT/ACTH	Event Number ACT/ACTH	Relative Risk (95% CI)	p value
FISH +	1,588 (789/799)	160/85	0.47 (0.36–0.61)	<0.0001
FISH -	207 (114/93)	23/8	0.40 (0.18–0.89)	0.026
IHC 3+	1,488 (740/748)	151/82	0.48 (0.37–0.63)	<0.0001
IHC- (0, 1+,2+)	299 (161/138)	32/10	0.32 (0.16–0.65)	0.0017
FISH- IHC-	174 (92/82)	20/7	0.34 (0.14–0.8)	0.014

CI = confidence interval; FISH = fluorescence in situ *hybridization; IHC = immunohistochemistry; AC = adriamcycin/cyclophosphamide.*
Results taken from the National Surgical Adjuvant Breast and Bowel Project B31 study. Reprinted with permission.

HER2 Status Determination

One of the most notable controversies of the past year pertains to HER2 status determination. Currently, HER2 status is determined by measuring HER2 protein expression by immunohistochemistry (IHC) and/or HER2 gene amplification by fluorescence *in situ* hybridization (FISH). A biologically plausible expectation is that increased levels of the HER2 receptor may confer amplified therapeutic benefit with trastuzumab therapy and, conversely, no significant benefit in the absence of HER2 gene amplification or protein overexpression. However, recent reports have challenged these expectations.

In the recent analysis of the central HER2 testing conducted in the large, randomized North American adjuvant trastuzumab trial NSABP B31, it appeared that the benefits seen with adjuvant trastuzumab may not be confined to patients with IHC 3+ and/or FISH-positive tumors.[32] In this study, women with IHC 3+ or FISH-positive HER2-positive breast cancer, as determined centrally or at an approved reference laboratory, were eligible to enroll.[26] On review, 174 of the 1,795 enrolled patients (9.7%) had breast cancers that were originally classified as HER2-positive but later classified as HER2-normal by IHC and FISH on central laboratory review. Despite these conflicting results, a consistent DFS benefit was observed in every subset of women on the study, including those women deemed HER2-normal on central laboratory review (RR 0.34; $p=0.014$) (see *Table 3*). It is challenging to reconcile these results with the reports of prior studies such as CALGB 9840, in which women with HER2-normal metastatic breast derived no benefit from trastuzumab therapy.[33] The critical distinction may be that the patients in CALGB 9840 were randomized only after their local laboratory first identified them as HER2-normal, while in the adjuvant trials, patients were first deemed HER2-positive by their local laboratories and later deemed HER2-normal centrally. Thus, one may postulate that the NSABP B31 data are a product of false-negative results on central laboratory testing, problems with specimen collection, hetereogeneity within the specimens provided for evaluation, or some other as yet undetermined biological explanation.

Until this matter of HER2 status determination is resolved, and given the significant survival benefits demonstrated in the adjuvant trastuzumab trials, it is reasonable to offer adjuvant trastuzumab to any woman whose breast cancer has ever been reported as HER2-positive. The American Society of Clinical Oncology (ASCO) published guidelines on this topic earlier this year.

Gene Expression Profiling

The cornerstone of adjuvant treatment recommendations for women with small, node-negative, ER-positive early-stage breast cancer is typically a hormone maneuver. As the additional benefit of systemic chemotherapy in this population is often uncertain and the potential treatment-related toxicity may be significant, recommendations regarding adjuvant chemotherapy are often challenging. To facilitate adjuvant therapy recommendations, several gene assays have recently been developed that stratify women into risk categories. For example, Oncotype DX® is a 21-gene assay that was developed and validated in two NSABP studies to facilitate risk profiling among women with node-negative, tamoxifen-treated, early-stage breast cancer.[34] Individual recurrence risk is stratified as low, intermediate, or high with associated 10-year distant recurrence rates of 6.8, 14.3, and 30.5%, respectively. Typically, hormone therapy alone is recommended for women with low-risk scores, while both hormone therapy and chemotherapy are recommended for women with high-risk scores. As the optimal treatment strategy for women at intermediate risk is uncertain, the TAILORRX trial is currently randomizing these women to hormone therapy alone or in combination with chemotherapy. In a recent study of the 21-gene assay among post-menopausal women with node-positive breast cancer treated with tamoxifen with or without cyclophosphamide/adriamycin/5-fluorouracil (CAF) chemotherapy, results proved consistent with those reported among the node-negative cohort.[35]

Conclusions

Recently, improvements in incidence rates in the US for some types of breast cancer have been reported. However, because a significant proportion of women with early-stage disease experience a relapse and die due to metastatic breast-cancer-related complications, therapeutic innovations continue to be explored. Recently, a number of innovations have been reported, particularly in taxane-containing and dose-dense adjuvant chemotherapy strategies. However, until all women with early-stage disease can be cured, ongoing innovations are anticipated. It is hoped that further insights into the pathophysiology of breast cancer subtypes will permit refinements to the treatment paradigm so that adjuvant therapy recommendations may be increasingly tailored to the biology of individual tumors. ■

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