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# The Evolving Adjuvant Treatment Landscape in Patients with Early Breast Cancer

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Breast cancer is the most common cancer in women in the USA and second only to lung cancer in mortality [1,2]. It is estimated that there will be 231,840 new cases of invasive breast cancer and 40,290 deaths from the disease in 2015. While the incidence of breast cancer has increased steadily in the United States through the 1980s, it has now stabilized at about 125 cases per 100,000 per year [3,4]. Breast cancer survival has significantly improved over the years, reflecting advances in effective local and systemic therapy. Moreover, adjuvant systemic therapy reduces the risk of distant recurrence presumably by treating micro-metastatic disease that may not be clinically evident at the time of definitive local therapy. While the benefit from endocrine and HER-2 directed therapy is predicted by the expression of their respective receptors [5,6], predicting response to chemotherapy remains a challenge. Several multi parameter gene expression assays have now been developed, which provide further prognostic information and more importantly predict benefit from adjuvant chemotherapy [5]. These assays will help tailor therapy towards patients who will derive greatest benefit from chemotherapy [6,7].

Endocrine therapy reduces the risk of breast cancer recurrence in hormone receptor positive disease, when used with or without chemotherapy. In 1982, 2-year adjuvant tamoxifen treatment was shown to reduce the risk of recurrence [8] and improve survival [9], with subsequent studies revealing that five-year tamoxifen therapy was more effective than shorter durations. Five-year tamoxifen decreased recurrence by about 40% and breast cancer mortality by 30%, interestingly the effect of tamoxifen was present not only during therapy (1-5 years) but also after tamoxifen was discontinued(carry-over effect) [10]. Tamoxifen risk reductions were substantial and consistent for women in each age range (including post-menopausal woman) [10]. First generation Aromatase inhibitors were too toxic in pivotal clinical trials and further development of third generation Aromatase inhibitors showed better toxicity profile and subsequently were found to improve DFS and OS when compared to tamoxifen in postmenopausal women [11,12]. Hormone receptor positive disease is known to have recurrence even beyond 5 years of diagnosis; therefore clinical trials with longer endocrine therapy were developed [13]. Extended adjuvant therapy for up to 10 years was shown to be more effective than 5 years of therapy, including sequential tamoxifen followed by an aromatase inhibitor [14], or tamoxifen for up to 10 years [15]. Finally, in premenopausal women at high risk for recurrence, ovarian suppression plus an aromatase inhibitor was shown to be more effective than tamoxifen [16,17].

Recently published article by Anampa et al. summarized the important landmark trials and recent advances in the evolution of adjuvant chemotherapy for early breast cancer [18]. The national surgical adjuvant breast and bowel project (NSABP) B-01 trial initiated in 1958, the first randomized trial evaluating adjuvant chemotherapy in breast cancer after local therapy, revealed that thiotepa significantly decreased recurrence rate in pre-menopausal women with ≥ 4 positive axillary lymph nodes [19]. Meanwhile, several combination regimens were being used for lymphoma with good outcomes such as MOPP regimen (mechlorethamine, vincristine, procarbazine and prednisone) that were used to treat patients with Hodgkin's disease [20], leading to the development of CMF (cyclophosphamide, Methotrexate and 5-FU) regimen with the intent to resemble the highly active MOPP regimen.

Bonadonna et al. from the Istituto Nazionale Tumori in Milan, Italy showed that CMF used after surgical resection significantly reduced the risk of breast cancer recurrence (HR 0.70) and mortality (HR 0.76) [21,22], leading to a new strategy in breast cancer management. In 2001, a national institute of health (NIH) consensus panel in the USA concluded that chemotherapy should be recommended to the majority of women with localized breast cancer regardless of lymph node, menopausal or hormone receptor status [23].

Anthracyclines were found to have significant effect in breast cancer cells. Therefore initial trials evaluated the combination of doxorubicin 60 mg/m$^2$ plus cyclophosphamide 600 mg/m$^2$ (AC) given every three weeks for total of four cycles, and at least two large clinical trials found similar DFS and OS when compared to six cycles of CMF in patients with node positive and negative disease [24,25].

Paclitaxel and docetaxel are the most common used taxanes in the management of breast cancer. Sequential addition of four cycles of every-3-week paclitaxel to four cycles of AC was found to have improved DFS (HR=83) and OS (HR=0.82) [26]. Docetaxel was found to be a more potent microtubule inhibitor than paclitaxel, therefore clinical trials evaluated docetaxel combined sequentially versus concurrently with doxorubicin/cyclophosphamide. Sequential docetaxel-AC improved DFS (HR=0.83) compared to concurrent docetaxel-AC [27].

Adjuvant! Online is a web-based decision aid used by many clinicians to understand the potential benefits of adjuvant therapy (endocrine or cytotoxic). Adjuvant! classifies chemotherapy regimens as first, second and third generation [28]. Third-generation (anthracycline and taxane containing) regimens are commonly used in patients with high recurrence-risk, given superior efficacy when compared to first or second generation regimens. First and second generation regimens still have an important role in clinical practice, such as situations when anthrayclines need to be avoided or for tumors with low/intermediate recurrence-risk. Dose density and intensity have been evaluated for

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different chemotherapy regimens. The optimal Taxane schedule was evaluated by the ECOG E1199 trial, in which patients treated with AC × 4 were assigned to receive paclitaxel or docetaxel every three weeks for four doses or weekly for 12 doses using a 2 × 2 design. After 12.1-year follow-up, DFS was significantly improved and OS marginally improved for both the weekly paclitaxel arm (HR 0.84, p=0.011 and HR 0.87, p=0.09, respectively) and every-3-week docetaxel arm (HR 0.79, p=0.001 and HR 0.86, p=0.054, respectively) when compared to the control arm (every-3-week paclitaxel). Although weekly paclitaxel improved DFS and OS (HR 0.69, p=0.010 and HR 0.69, p=0.019, respectively) in triple negative breast cancer, no experimental arm improved OS for hormone receptor positive, HER2 non-overexpressing breast cancer [29].

One major challenge with the evolution of the adjuvant chemotherapy in breast cancer is to decide about whether or not to use it; as despite the reduced recurrence rates and mortality it is associated with considerable adverse effects. Gene expression profiling is an emerging technology for identifying genes whose activity may be helpful in assessing disease prognosis and guiding therapy. In recent years, several multiparameter gene expression profiling assays have been shown to provide prognostic information in patients with ER-positive breast cancer [6,7], these assays include the Oncotype DX® (Genomic Health, Inc., Redwood City, CA), MammaPrint® (Agendia, Inc. USA, Irvine, CA), Prosigna® (Nanostring Technologies, Seattle, WA), and Breast Cancer Index℠ (bioTheranostics, Inc., San Diego, CA). TAILORx, MINDACT, RxPONDER, and OPTIMA trials are evaluating the incorporation of multiparameter gene expression assays into clinical decision making to tailor adjuvant treatment among patients with breast cancer.

HER2 oncogene expression is present in about 25% patients with breast cancer [30]. Trastuzumab, a monoclonal antibody which binds to HER2 domain IV initially approved in 2006 after analysis of NSABP B31 and NCCTG N9831 studies, shows substantially decreased risk of recurrence in patients with HER2 overexpressing node-positive or high-risk node-negative breast cancer [31-34]. Addition of trastuzumab to sequential anthracycline/cyclophosphamide-taxane was associated with about a 3-5% risk of cardiac toxicity [31-33], while the combination of trastuzumab with non-anthracycline regimens (e.g. carboplatin/docetaxel), was associated with lower rates of cardiac toxicity [34]. Subsequent studies demonstrated that one year of trastuzumab was more effective than 6 months [35], but two years of therapy was no more effective than one year [36]. Pertuzumab, a monoclonal antibody which binds to HER-2 extracellular domain II, has shown improved complete pathological response rates when used in the neoadjuvant setting in NEOSPHERE/TRYPHAENA trials [37], and currently being evaluated in the adjuvant setting as per APHINITY trial. The current version of NCCN guidelines allow adjuvant Petuzumab-containing regimens in patients with high risk HER2 positive disease (T2 or greater, and N1 or greater) Bone is one of the most common sites of breast cancer recurrence, and bisphosphonates have been shown to exert anticancer effects and alter the microenvironment. Clodronate and zolendronic acid were used as adjuvant therapy in patients with early breast cancer. A recent meta-analysis included 17709 women treated with adjuvant bisphosphonates and revealed a significant improvement in bone recurrence in the entire study population. (HR=0.83), sub-group analysis showed that adjuvant bisphosphonates improved also distant recurrence and breast cancer mortality (HR=0.82) among postmenopausal women [38].

Denosumab, a fully human IgG2 monoclonal antibody that binds to RANK ligand, is an essential mediator of osteoclast activity. The ABCSG-18 trial evaluated the role of adjuvant denosumab 60mg subcutaneously every 6 months versus placebo in 3420 patients with early hormone-receptor positive breast cancer receiving aromatase inhibitors. Patients in the denosumab group had significant decrease in fracture risk (HR=0.50, p<0.0001). In the recent San Antonio Breast Cancer Symposium 2015, the study group reported an improved DFS (HR=0.816, 95%CI 0.66-1.00, p 0.0515) favoring the denosumab arm.

In conclusion, medical oncologists need to carefully select patients for adjuvant therapy based on tumor-specific factors (tumor size, axillary node metastasis) and tumor biology (ER/PR and HER2 expression, multiparameter gene expression assays), and patient specific factors such as age, comorbidities and patient preference. A risk classification and potential therapeutic options for each risk category are proposed in Table 1. Improvements in adjuvant cytotoxic regimens have contributed to declining breast cancer mortality rates in recent years, and ongoing clinical trials may identify subgroups with greatest benefits from such therapy. Further results on clinical trials evaluating HER2 directed therapies, bisphosphonates and denosumab are expected to increase the available therapeutic options for management of patients with early breast cancer.

| Recurrence Risk Category and Definition | Recommended Regimens: ER positive, HER2-Negative | Recommended Regimens: ER/PR negative, HER2-Negative | Recommended Regimens: HER2-Positive |
|---|---|---|---|
| **Very Low Risk** | | | |
| • Node-Neg, T1a | No chemotherapy | No chemotherapy | No chemotherapy |
| **Low Risk** | | | |
| • Node-Neg, T1b | Consider 2nd generation chemotherapy regimen if RS is high | Consider 2nd generation chemotherapy regimen | Consider weekly paclitaxel + H |
| • Node-Neg, T1c, | 2nd generation chemotherapy regimen if RS is high (or consider if intermediate) | 2nd generation chemotherapy regimen | Weekly paclitaxel + H or TCH |
| **Moderate Risk** | | | |
| • Node-Neg, T2 | 2nd or 3rd generation chemotherapy regimen if RS intermediate-high | 3rd generation chemotherapy regimen | AC-T+H or TCH +/- P |
| **High Risk**<br>• +Pos Nodes or T3 | 3rd generation chemotherapy regimen if RS intermediate-high (or 4+ positive nodes irrespective of RS) | 3rd generation chemotherapy regimen | AC-T+H or TCH+/-P |
| TCH: Docetaxel, Carboplatin, Trastuzumab; T: paclitaxel; AC: Doxorubicin, Cyclophosphamide; H: Trastuzumab, P: Pertuzumab. Neg: Negative. Pos: Positive; RS: Recurrence score. | | | |

**Table 1:** Commonly recommended adjuvant chemotherapy regimens [18].

| Year | Event | Reference |
|---|---|---|
| 1894 | Halsted introduced radical mastectomy for breast cancer. | Ann Surg. 1894; 20:497-555. |
| 1950s | Anthracyclines isolated from gram-positive Streptomyces in Indian soil samples. | Drugs, 1997. 54(4): 1-7. |
| 1968 | NSABP B-01. Thiotepa after radical mastectomy decreased recurrence rate and OS.[a] | Fisher, et al. [19] |
| 1969 | Paclitaxel is isolated after an exploratory plant screening program. | Med Res Rev, 1998; 18: 315-331. |
| 1974 | Doxorubicin shows activity against breast cancer cells. | Br J Cancer. 1974; 29: 114-116. |
| 1975 | Melphalan shows improved DFI as adjuvant after mastectomy.[b] | N Engl J Med 1975; 292:117-122 |
| 1976 | CMF ×12 shows decreased rate failure compared to control (no chemotherapy).[c] | Bonadonna, et al. [22] |
| 1979 | CMF × 6 vs CMF × 12 have similar DFS and OS.[d] | Cancer Clin Trials 1979; 2: 285-292. |
| 1979 | Horwitz demonstrated mechanism of action of paclitaxel. | Med Res Rev, 1998. 18: 315-31. |
| 1983 | Tamoxifen improves survival in patients with early breast cancer | Baum, et al. [9] |
| 1990 | NSABP B-15: AC × 4 vs CMF × 6 revealed similar OS or DFS in node + disease.[e] | Fisher, et al. [24] |
| 2001 | NSABP B-23. No difference in OS for AC × 4 and CMF × 6 in node negative patients.[f] | Fisher, et al. [25] |
| 2001 | NIH consensus recommended adjuvant chemotherapy for patients with early breast cancer. | Abrams [23] |
| 2001 | Five years of adjuvant Tamoxifen therapy is more effective than shorter durations.[g] | Cochrane Database Syst Rev, 2001; 1: CD00486 |
| 2003 | CALGB 9741: Dose density improves DFS and OS.[h] | J Clin Oncol, 2003; 21: 1431-9 |
| 2003 | INT 0148/CLGB 9344 : Sequential paclitaxel after AC improved DFS and OS.[i] | Henderson, et al. [26] |
| 2004 | Oncotype Dx validated in NSABP B-14 /B-20 studies. | N Engl J Med, 2004; 351: 2817-2826. |
| 2005 | Trastuzumab combined to paclitaxel after AC, improves DFS and OS in HER2 overexpressing disease. [j] | Romond EH, et al.[31] |
| 2005 | Aromatase inhibitors more effective than Tamoxifen in postmenopausal women.[k] | Breast International Group 1-98 Collaborative [12] |
| 2006 | US oncology 9735: TC × 4 has improved DFS compared to AC × 4.[l] | J Clin Oncol. 2006; 24: 5381-5387. |
| 2008 | ECOG 1199: Weekly sequential paclitaxel after AC improves DFS and OS.[m] | N Engl J Med, 2008; 358: 1663-1671. |
| 2013 | One year adjuvant trastuzumab is as effective as 2 years in HER2 overexpressing disease.[n] | Goldhirsch A, et al. [36] |
| 2013 | Pertuzumab combined with trastuzumab based chemotherapy improves pCR in HER2 locally advanced breast cancer | Schneeweiss, et al. [37] |
| 2013 | Extended adjuvant Tamoxifen up to 10 years more effective than 5 years therapy.[o] | Davies, et al. [15] |
| 2014 | Ovarian suppression and aromatase inhibitor (exemestane) more effective than tamoxifen and ovarian suppression in premenopausal women.[p] | Pagani, et al. [17] |

DFI: Disease-free interval; OS: Overall survival; DFS: Disease-free survival; RFS: Recurrence-free survival; EFS: vent-free survival; DDFS: Distant disease-free survival; pCR: Pathological complete response;
a. Thiotepa improved 5-year survival rate (57%vs 24%, p<0.05) in pre-menopausal women with four or more positive LN compared to placebo. b. Treatment failure 22 %( placebo) and 9.7 % (Melphalan), p=0.01. Disease-free interval showed statistically significant difference (p=0.02) in favor of Melphalan. c. Treatment failure (25 vs 5.3%, p<0.00001) for control and CMF respectively. d. 3-year RFS survival was 85.4% (CMF x12) compared to 82.6% (CMF x6), P=0.29.OS 86.2% vs. 85.1%, P=0.49. e. No difference in 3-year DFS (P=0.5), distant disease-free survival (DDFS, P=0.5) or survival (P =0 .8) between both groups. f. No significant difference for CMF and AC in RFS (87% both groups, P=0.9), EFS (83% and 82%, P=0.6), or survival (89% and 90%, P=0.4). g. With 5 years of Tamoxifen use absolute improvement in 10-year survival was 10.9% for node-positive and 5.6% for node-negative, compared to 1 and 2 years. h. Dose-dense improved DFS (RR=0.74; P=.010), and OS (RR=0.69; P=.013). There was no difference in either DFS or OS between the concurrent and sequential schedules. i. Hazard reductions from adding paclitaxel to AC were 17 % for recurrence (adjusted Wald $\chi 2$ P=.0023; unadjusted Wilcoxon P=.0011) and 18% for death (adjusted P=.0064; unadjusted =.0098). j. DFS HR 0.48, P<0.0001, OS HR 0.67, p=0.015, favoring Trastuzumab vs control.
k. Compared to tamoxifen, letrozole significantly reduced the risk of distant recurrence; HR 0.73, 95% CI: 0.7-0.93, P = 0.003). l. 5-year DFS TC (86%) compared with AC (80%); HR=0.67; 95% CI, 0.50 to 0.94; P=0.015. m. As compared with patients receiving q-3-week paclitaxel, the odds ratio for 5-year DFS was 1.27 among those receiving weekly paclitaxel (P=0.006), OS also favored weekly paclitaxel (odds ratio, 1.32; P=0.01). n. One year of adjuvant trastuzumab provided comparable DFS and OS benefits as compared to 2 years. o. Continuing Tamoxifen up to 10 years further reduced recurrence and mortality, as compared to 5 years therapy. p. Adjuvant exemestane with ovarian suppression significantly reduced recurrence compared to tamoxifen with ovarian suppression; with DFS at 5-years: 91.1% in exemestane arm compared to 87.3% in Tamoxifen arm.

**Table 2:** Timeline of adjuvant therapy for breast cancer.

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