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 thiopeta 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/m2 plus cyclophosphamide 600 mg/m2 (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=0.83) 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 anthracyclines need to be avoided or for tumors with low/intermediate recurrence-risk. Dose density and intensity have been evaluated for...
different chemotherapy regimens. The optimal Taxane schedule was evaluated by the ECOG E1199 trial, in which patients treated with AC \times 4 were assigned to receive paclitaxel or docetaxel every three weeks for four doses or weekly for 12 doses using a 2 \times 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 (Agenda, Inc. USA, Irvine, CA), Prosigina (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 recurrence in patients with HER2 overexpressing node-positive or T3 respectively) in triple negative breast cancer, no experimental arm improved OS for hormone receptor positive, HER2 non-overexpressing breast cancer [29].

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

<table>
<thead>
<tr>
<th>Recurrence Risk Category and Definition</th>
<th>Recommended Regimens: ER positive, HER2-Negative</th>
<th>Recommended Regimens: ER/PR negative, HER2-Negative</th>
<th>Recommended Regimens: HER2-Positive</th>
</tr>
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<tbody>
<tr>
<td>Very Low Risk</td>
<td>No chemotherapy</td>
<td>No chemotherapy</td>
<td>No chemotherapy</td>
</tr>
<tr>
<td>Low Risk</td>
<td>Consider 2nd generation chemotherapy regimen if RS is high</td>
<td>Consider 2nd generation chemotherapy regimen if RS is high</td>
<td>Weekly paclitaxel + H or TCH</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>2nd generation chemotherapy regimen if RS is high (or consider if intermediate)</td>
<td>2nd generation chemotherapy regimen if RS is high (or consider if intermediate)</td>
<td>AC-T+H or TCH +/- P</td>
</tr>
<tr>
<td>High Risk</td>
<td>3rd generation chemotherapy regimen if RS intermediate-high (or 4+ positive nodes irrespective of RS)</td>
<td>3rd generation chemotherapy regimen if RS intermediate-high (or 4+ positive nodes irrespective of RS)</td>
<td>AC-T+H or TCH+/-P</td>
</tr>
<tr>
<td>+Pos Nodes or T3</td>
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</table>

TCH: Docetaxel, Carboplatin, Trastuzumab; T: paclitaxel; AC: Doxorubicin, Cyclophosphamide; H: Trastuzumab; P: Pertuzumab. Neg: Negative. Pos: Positive; RS: Recurrence score.
Fisher, et al. [24]
Goldhirsch A, et al. [36]
J Clin Oncol. 2006; 24: 5381-5387.
Melphalan shows improved DFI as adjuvant after mastectomy. [4]
Extended adjuvant Tamoxifen up to 10 years more effective than 5 years therapy.
Halsted introduced radical mastectomy for breast cancer.
Oncotype Dx validated in NSABP B-14 /B-20 studies.

1000e1
Ovarian suppression and aromatase inhibitor (exemestane) more effective than tamoxifen and ovarian suppression
Bonadonna, et al. [22]
Davies, et al. [15]
US oncology 9735: TC × 4 has improved DFS compared to AC × 4.
Five years of adjuvant Tamoxifen therapy is more effective than shorter durations.

Pertuzumab combined with trastuzumab based chemotherapy improves pCR in HER2 locally advanced breast cancer.
CALGB 9741: Dose density improves DFS and OS. [o]
NIH consensus recommended adjuvant chemotherapy for patients with early breast cancer.
CMF × 6 vs CMF × 12 have similar DFS and OS. [d]
CMF × 6 vs CMF × 12 revealed similar OS or DFS in node + disease. [a]

One year adjuvant trastuzumab is as effective as 2 years in HER2 overexpressing disease. [j]
CMF × 6 vs CMF × 12 have similar DFS and OS.
CMF ×12 shows decreased rate failure compared to control (no chemotherapy). [i]

Bonadonna, et al. [22]

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Table 2: Timeline of adjuvant therapy for breast cancer.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Reference</th>
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<tr>
<td>1968</td>
<td>NSABP B-01. Thiopeta after radical mastectomy decreased recurrence rate and OS. [a]</td>
<td>Fisher, et al. [19]</td>
</tr>
<tr>
<td>1976</td>
<td>CMF ×12 shows decreased rate failure compared to control (no chemotherapy). [i]</td>
<td>Bonadonna, et al. [22]</td>
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<tr>
<td>1990</td>
<td>NSABP B-15: AC × 4 vs CMF × 6 revealed similar OS or DFS in node + disease. [a]</td>
<td>Fisher, et al. [24]</td>
</tr>
<tr>
<td>2001</td>
<td>NSABP B-23. No difference in OS for AC × 4 and CMF × 6 in node negative patients. [i]</td>
<td>Fisher, et al. [25]</td>
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<tr>
<td>2001</td>
<td>NIH consensus recommended adjuvant chemotherapy for patients with early breast cancer.</td>
<td>Abrams [23]</td>
</tr>
<tr>
<td>2005</td>
<td>Five years of adjuvant Tamoxifen therapy is more effective than shorter durations. [o]</td>
<td>Cochrane Database Syst Rev, 2001; 1: CD00488</td>
</tr>
<tr>
<td>2005</td>
<td>Trastuzumab combined to paclitaxel after AC, improves DFS and OS in HER2 overexpressing disease. [j]</td>
<td>Romond EH, et al.[31]</td>
</tr>
<tr>
<td>2005</td>
<td>Aromatase inhibitors more effective than Tamoxifen in premenopausal women. [a]</td>
<td>Breast International Group 1-98 Collaborative [12]</td>
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<tr>
<td>2013</td>
<td>One year adjuvant trastuzumab is as effective as 2 years in HER2 overexpressing disease. [j]</td>
<td>Goldhirsch A, et al. [36]</td>
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<td>2013</td>
<td>Pertuzumab combined with trastuzumab based chemotherapy improves pCR in HER2 locally advanced breast cancer</td>
<td>Schneeweiss, et al. [37]</td>
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<td>Extended adjuvant Tamoxifen up to 10 years more effective than 5 years therapy.</td>
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<td>Ovarian suppression and aromatase inhibitor (exemestane) more effective than tamoxifen and ovarian suppression in premenopausal women. [a]</td>
<td>Pagani, et al. [17]</td>
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References:


