New paradigms in adjuvant systemic therapy of breast cancer

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Abstract
Since the initial studies of adjuvant therapy in the 1970s, it has become increasingly clear that chemotherapy and hormone therapy have had a substantial effect on the survival of women with early breast cancer. It was originally assumed that only women with high-risk features would derive benefit from adjuvant therapy, but it is now apparent from numerous studies that adjuvant therapy improves survival in all subgroups of women with invasive breast cancer, although the absolute benefit varies depending on tumor stage and other prognostic features. Considerable progress has been made in elucidating effective adjuvant therapy regimens, but there continue to be many unanswered questions that are being addressed in ongoing clinical trials of adjuvant hormone therapy and chemotherapy. This paper reviews the current paradigms in adjuvant therapy, the published data that have affected current practice patterns, and the current controversies.

Introduction
An estimated 192,200 women were diagnosed with invasive breast cancer in 2001, and approximately 40,200 died from it. Breast cancer is the most common cancer among women in the United States and other industrialized nations and is the second most common cause of cancer death (Greenlee et al. 2001). The use of tamoxifen, ovarian ablation and chemotherapy in the adjuvant setting have revolutionized the treatment of early breast cancer and substantially improved survival. These benefits are long-lasting, exceeding 15–20 years. The optimal use and sequence of adjuvant therapy interventions reduce the risk of recurrence and death by more than 50%. However, many women still die from their disease despite these advances.

Tamoxifen has been the gold standard for adjuvant therapy for hormone receptor-positive breast cancer for decades. However, aromatase inhibitors have demonstrated substantial efficacy and tolerability in patients with metastatic disease and in the adjuvant setting and may supplant tamoxifen for postmenopausal women, leading to a significant paradigm shift. Ongoing trials are evaluating the most appropriate duration of tamoxifen therapy and the sequential use of aromatase inhibitors. Adjuvant chemotherapy regimens that have been studied have varied from a single perioperative cycle to 2 years of therapy. The available data indicate that 4–6 months of chemotherapy is the most effective, yet many questions remain unanswered. In this paper we summarize the current standards of care in adjuvant therapy, the influential studies, and the current controversies, including the incorporation of taxanes, sequential vs simultaneous combination regimens, inclusion of trastuzumab (Herceptin) and the current status of high-dose therapy.

Adjuvant hormone therapy
Meta-analyses of adjuvant tamoxifen trials by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) have repeatedly demonstrated highly significant reductions in recurrence and mortality with the use of tamoxifen (Early Breast Cancer Trialists’ Collaborative Group 1988, 1992, 1998). Tamoxifen, when administered for 5 years to women with estrogen receptor (ER)-positive breast cancer in the adjuvant (postoperative) setting, reduces the risk of recurrence by 47% and mortality by 26% based on the most recent overview analysis (Early Breast Cancer Trialists’ Collaborative Group 1998a). These benefits were seen regardless of the patients’ age, menopausal status or axillary nodal status. Until recently, it has been unclear whether premenopausal patients or those with ER-negative tumors would benefit from adjuvant hormone therapy. This is addressed further below. Ongoing trials are addressing the role of combined and sequential hormone therapy with tamoxifen and aromatase inhibitors, which should further define the effect of these agents on survival in patients with early breast cancer.
Age

The initial EBCTCG meta-analysis of adjuvant tamoxifen trials (Early Breast Cancer Trialists’ Collaborative Group 1988) did not demonstrate a clear survival benefit for women younger than 50 years old. Although 28 trials were included in the meta-analysis, only 3652 women made up this age group. In addition, there was tremendous heterogeneity among the trials in duration of tamoxifen use (<1 year vs >2 years) and availability of ER status data. In fact, the ER status was documented in only 50% of patients included in the analysis and was determined by ligand-binding assay rather than by currently used immunohistochemical assays. The subsequent overview, published in 1992, found a similar absence of benefit in this age group (Early Breast Cancer Trialists’ Collaborative Group 1992). Despite the limitations of these early studies, physicians did not routinely recommend that patients younger than 50 years old receive adjuvant tamoxifen therapy. However, there was clearly a substantial reduction in mortality among women older than 50 years who took it.

In stark contrast to these earlier meta-analyses, the most recent EBCTCG overview analysis (Early Breast Cancer Trialists’ Collaborative Group 1998a) showed a comparable reduction in mortality among all women taking adjuvant tamoxifen, irrespective of age. This analysis included 37,000 women in 55 trials. It is now considered the standard of care to recommend adjuvant tamoxifen to all women with ER-positive invasive breast cancers.

ER status

Most adjuvant tamoxifen trials included in the EBCTCG meta-analyses did not rigorously exclude patients with ER-negative tumors and there has been some controversy about whether tamoxifen might benefit this subset of patients. Preclinical experiments demonstrated multiple additional biological effects of tamoxifen that are not mediated through the ER signaling pathway. These provided the theoretical underpinnings of this controversy. The most recent published analysis (Early Breast Cancer Trialists’ Collaborative Group 1998a) and the updated but unpublished 2000 Oxford Overview meta-analysis have demonstrated that adjuvant tamoxifen in patients with ER-negative tumors provides no benefit in mortality or contralateral breast cancer reduction. Some have contended that the use of tamoxifen may reduce the likelihood of a patient with ER-negative cancer developing a new cancer that is ER-positive. Data from three National Surgical Adjuvant Breast and Bowel Project (NSABP) trials (B-18, B-22 and B-25) were recently analyzed to assess the association between the ER status of a patient’s initial tumor and that of a new contralateral breast cancer (Swain et al. 2002). The analysis showed a strong correlation, particularly in the ER-negative subset. Among patients with ER-negative tumors at diagnosis, those younger than 50 years and those over 50 were equally as likely to develop a second ER-negative tumor, 68 and 75% respectively. Fewer than one-third of these patients with an ER-negative initial tumor developed a new primary tumor that was ER-positive. These data support the rationale for the lack of benefit of adjuvant tamoxifen in ER-negative patients.

Duration of hormone therapy

All EBCTCG overviews have shown that the benefits of tamoxifen increase for each year of treatment for up to 5 years but that there is no clear benefit beyond 5 years. Results of three published randomized trials, described below, have specifically addressed the issue of 5 years vs longer duration of tamoxifen.

The NSABP B-14 trial (Fisher et al. 1996a, 2001a) randomized 1152 patients with ER-positive, node-negative disease who had already received 5 years of tamoxifen therapy to receive an additional 5 years of treatment with either placebo or tamoxifen. At nearly 7 years of follow-up, there was a significant disadvantage associated with prolonged tamoxifen use with a disease-free survival (DFS) of 82% in the placebo group and 78% in the additional tamoxifen group \((P=0.03)\). As expected, twice the number of endometrial carcinomas occurred among those randomized to continue treatment with tamoxifen.

A randomized trial conducted by the Scottish Cancer Trials Breast Group (Stewart et al. 1996, 2001) compared 5 years vs indefinite tamoxifen therapy in 342 patients. Only 39% of accrued patients were known to have ER-positive tumors. At 10 years of follow-up, there was a non-significant trend toward inferior outcomes in patients treated with the longer duration of tamoxifen. When the data were reanalyzed to evaluate only the women with ER-positive breast cancer, no significant differences were found between the treatment groups. Similar to the findings in the NSABP B-14 study, there was a higher incidence of endometrial cancers in the patients given prolonged treatment.

The third published study evaluating a longer duration of tamoxifen therapy combined patients from two Eastern Cooperative Oncology Group (ECOG) studies, E 4181 and E 5181, who had undergone chemotherapy for node-positive disease. One hundred and ninety-three patients were included. 73% of whom had ER-positive tumors \((\geq 10 \text{ fmol/mg})\) as determined by ligand-binding assay. At more than 5 years of follow-up, there was a non-significant trend of benefit in time to first recurrence in favor of prolonged therapy. When analysis was limited to the ER-positive cohort, the improved time to first recurrence or contralateral primary did reach statistical significance with no difference in overall survival (OS). Longer follow-up from this study reportedly shows no significant difference in DFS or OS between the treatment arms (Bryant et al. 2001).
Aromatase inhibitors

The aromatase inhibitors anastrozole and letrozole and the aromatase inactivator exemestane have demonstrated equivalent or superior efficacy over that of tamoxifen in metastatic disease and have improved side-effect profiles. It is therefore logical to incorporate these agents into adjuvant therapy trials for ER-positive breast cancer. Numerous ongoing trials are comparing tamoxifen alone with combined or sequential therapy with varying durations of aromatase inhibitor therapy (Table 1). The first published adjuvant study involving an aromatase inhibitor is the arimidex, tamoxifen, alone or in combination trial, which is the largest therapeutic breast cancer trial ever conducted (ATAC (Arimidex, Tamoxifen, or in Combination) Trialists’ Group 2002). The 9366 accrued postmenopausal patients were randomized in a double-blind fashion to receive anastrozole, tamoxifen or a combination of both drugs for 5 years. In an intent-to-treat analysis at 33 months of follow-up, the 3-year DFS was statistically superior for those treated with anastrozole alone compared with those treated with tamoxifen alone or the combination, 89 vs 87% respectively (P = 0.013). Only 16% of patients had ER-negative or unknown disease and when this cohort was separately analyzed, there was no impact on DFS by any of the hormone therapies. There was a substantial decrease in the number of contralateral breast cancers among those taking anastrozole alone compared with those taking tamoxifen alone or the combination. In fact, among those taking anastrozole alone, an additional 58% reduction occurred in contralateral breast tumors compared with that in patients taking only tamoxifen or the combination. Significantly fewer thromboembolic events, endometrial cancers, episodes of vaginal bleeding and hot flashes were reported in those taking anastrozole alone compared with those in the other treatment groups. There was a higher incidence of musculoskeletal discomfort and fractures in the patients taking anastrozole alone. Longer follow-up is necessary to assess the effect of anastrozole on OS. These data make it reasonable to consider anastrozole for adjuvant therapy in postmenopausal patients with ER-positive invasive breast cancer. As a result of these data, the US Food and Drug Administration has recently approved anastrozole for adjuvant therapy in postmenopausal patients. The American Society of Clinical Oncology has recently published recommendations on the use of adjuvant anastrozole on the basis of the opinions of a panel of oncologists who assessed the current data on aromatase inhibitors. Their recommendation was that tamoxifen should continue to be the standard of care for adjuvant hormone therapy in the absence of relative contraindications for tamoxifen, such as thromboembolic risk factors. For those with contraindications to tamoxifen, anastrozole is appropriate therapy (Winer et al. 2002).

Ovarian ablation

Ablation of the ovaries is the oldest form of systemic therapy for early breast cancer. Ovarian ablation can be achieved with surgical resection, irradiation or medical suppression with a luteinizing hormone-releasing hormone agonist. The EBCTCG overview of ovarian ablation as adjuvant therapy included 12 randomized trials of 2101 women younger than 50 years old (Early Breast Cancer Trialists’ Collaborative Group 1996). At 15 years of follow-up the DFS was significantly higher in those treated with ovarian ablation than in those who did not undergo it, 45 vs 39% respectively (P = 0.0007). The OS was similarly improved at 52 vs 46% (P = 0.001). Ovarian ablation did not provide a survival benefit in women who were older than 50 years at the start of the study.

In both the EBCTCG meta-analysis and a recent study that compared ovarian ablation plus chemotherapy with chemotherapy alone, ovarian ablation did not substantially improve the benefits resulting from chemotherapy alone (Early Breast Cancer Trialists’ Collaborative Group 1996, Rivkin et al. 1996). However, when the combination of tamoxifen, ovarian ablation, and chemotherapy was compared with chemotherapy alone, the combination proved superior (Davidson et al. 1999). But it is unknown whether this benefit was due to the combination of hormone interventions, or the tamoxifen alone.

Ovarian ablation alone has been compared with cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy in premenopausal women. A Scottish trial compared classic CMF and ovarian ablation and demonstrated comparable DFS and OS among the 332 randomized patients (Scottish Cancer Trials Breast Group 1993). A larger study of 732 premenopausal high-risk patients demonstrated that CMF and ovarian ablation were similarly effective (Ejlertsen et al. 1999). In addition, an Italian study comparing ovarian ablation plus tamoxifen to CMF demonstrated comparable survival rates (Boccardo et al 2000). Thus, it appears that ovarian ablation may be equivalent to CMF in premenopausal women with ER-positive disease, but ovarian ablation has not been directly compared with anthracycline-based therapy.

Taken together, these data demonstrate the important effect of ovarian ablation on survival in premenopausal patients with ER-positive tumors. Whether ovarian ablation adds to the benefits of chemotherapy or 5 years of tamoxifen remains to be clarified by ongoing clinical trials. The planned suppression of ovarian function trial will randomize patients to undergo tamoxifen alone, ovarian ablation plus tamoxifen, or...
Table 1 Ongoing adjuvant trials incorporating aromatase inhibitors

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment schema</th>
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<tbody>
<tr>
<td>ARNO</td>
<td>Tamoxifen × 2 years → anastrazole × 3 years</td>
</tr>
<tr>
<td>BIG-FEMTA</td>
<td>Randomize → letrozole × 5 years → tamoxifen × 5 years → letrozole 5 years → tamoxifen × 5 years</td>
</tr>
<tr>
<td>MA-17</td>
<td>Tamoxifen × 5 years → letrozole × 5 years → placebo × 5 years</td>
</tr>
<tr>
<td>Worldwide Intergroup</td>
<td>Randomize → tamoxifen × 5 years → tamoxifen × 2–3 years → exemestane × 2–3 years</td>
</tr>
<tr>
<td>NSABP B–33</td>
<td>Tamoxifen × 5 years → exemestane x 2 years → placebo × 2 years</td>
</tr>
</tbody>
</table>

ARND, Arimidex Nolvadex; BIG-FEMTA, Breast International Group Femara Tamoxifen; MA, Mammary.

Chemohormonal therapy

The most recent EBCTCG meta-analyses (Early Breast Cancer Trialists’ Collaborative Group 1998a,b) have demonstrated that hormone therapy and chemotherapy substantially increase survival compared with no systemic therapy. In addition, the combination of both modalities further increases the benefit compared with either therapy alone (Boccardo et al. 1992, Wils et al. 1999). The Ludwig III trial randomized 463 postmenopausal, node-positive patients to 1 year of CMF with prednisone and tamoxifen, 1 year of prednisone and tamoxifen or surgery alone. Both groups receiving adjuvant therapy fared better than those receiving surgery alone, but those receiving chemotherapy plus tamoxifen achieved statistically superior survival rates. At 13 years of follow-up (Castiglione-Gertsch et al. 1994), the DFS for the combined group was 35 vs 25% for the tamoxifen group and 14% for the surgery-alone group. The NSABP B-16 trial (Fisher et al. 1990) assessed the role of combined therapy by randomizing 1124 postmenopausal patients with node-positive disease to receive tamoxifen alone, doxorubicin with cyclophosphamide and tamoxifen (ACT), or melphalan, fluorouracil, doxorubicin and tamoxifen (PAFT). DFS was significantly improved for those receiving PAFT or ACT compared with tamoxifen alone, 84 vs 67% (P = 0.0004). Subsequently, the NSABP B-20 trial studied the worth of adding chemotherapy to tamoxifen for 2300 women with node-negative, hormone receptor-positive tumors. Patients were randomized to receive methotrexate and fluorouracil (MF) or CMF (both with tamoxifen) or tamoxifen alone. At 8 years of follow-up (Fisher et al. 2001b), DFS was superior among patients who received chemotherapy with tamoxifen compared with tamoxifen alone (84 vs 77%, P = 0.001). Similarly, OS was also higher for those who received chemotherapy (92 vs 88%, P = 0.018). A Canadian study compared tamoxifen with i.v. CMF plus tamoxifen and demonstrated no differences in survival rates (Pritchard et al. 1997). However, tamoxifen was administered for only 2 years, which was shown in the EBCTCG overview to be inferior to 5 years of therapy (Early Breast Cancer Trialists’ Collaborative Group 1998).

Until recently, whether tamoxifen and chemotherapy should be administered sequentially or concurrently was unclear. Preclinical data have demonstrated that endocrine therapy slows tumor growth, which may make tumor cells less susceptible to cell cycle-specific cytotoxic agents (Osborne et al. 1983, 1984, 1985, 1987). The combination of tamoxifen and chemotherapy has also been associated with an increased incidence of thromboembolic events. The Canadian study comparing tamoxifen alone with CMF plus
tamoxifen noted that 13.6% of those women allocated to receive combination therapy developed a thromboembolic event, in contrast to only 2.6% of those allocated to receive tamoxifen alone (Pritchard et al. 1996). The Intergroup 0100/Southwest Oncology Group 8814 trial directly addressed the issue of sequential vs concurrent therapy by randomizing women to receive tamoxifen alone, cyclophosphamide, doxorubicin, fluorouracil (CAF) followed by tamoxifen, or CAF plus tamoxifen. Although patients in both chemotherapy groups achieved superior survival compared with those treated with tamoxifen alone, there was a significant advantage for those who underwent the sequential treatment (Albain et al. 2002). At 8 years of follow-up, the DFS was 67% for the patients treated sequentially compared with 62% for those treated with concurrent chemotherapy and tamoxifen ($P = 0.045$). For these reasons, administering hormone therapy after chemotherapy for patients with ER-positive tumors should be considered standard therapy.

**Benefits of adjuvant chemotherapy**

Early studies of adjuvant chemotherapy were conducted among women thought to be at the highest risk for developing distant metastases, such as those with axillary lymph node involvement and ER-negative tumors (Bonadonna et al. 1976, Fisher et al. 1989, 1996b). Additionally, many investigators thought that chemotherapy would be effective only among young, premenopausal women, and these early studies did demonstrate substantial benefit in these subsets. However, it is now evident that the vast majority of patients with invasive breast cancer will derive benefit from systemic adjuvant therapy. The EBCTCG has conducted worldwide meta-analyses (the Oxford Overviews) of all randomized adjuvant chemotherapy trials to evaluate the quantitative benefit of systemic therapy among specific subsets of patients with invasive breast cancer (Early Breast Cancer Trialists’ Collaborative Group 1988, 1992, 1998b). The most recent 1998 Oxford Overview demonstrated substantial benefit for all patients regardless of their age, axillary nodal status, ER status and menopausal status, although the absolute benefit for each patient depends on her initial risk of recurrence. The 2000 Oxford Overview data have been presented and demonstrate similar benefits, but have not yet been published.

With respect to age, women younger than 40 years derive the greatest reduction in risk of recurrence from systemic polychemotherapy (37%), but even women aged 60–69 years old achieve a statistically significant risk reduction of 18% (Early Breast Cancer Trialists’ Collaborative Group 1998b). Similarly, death from breast cancer is delayed in all age groups, although a higher relative reduction is seen among those younger than 40 years old compared with those 60–69 years old, 27 vs 8% respectively. Few patients older than 70 years were included in the adjuvant studies analyzed and, therefore, no firm conclusions were made in the Overview for this age group. However, it is essential that comorbid conditions, rather than chronological age, dictate the use of adjuvant chemotherapy, given the wealth of data supporting the benefits of this modality.

ER status did not affect the substantial benefits provided by adjuvant chemotherapy, although the magnitude of benefit depended on age. In women younger than 50 years old who had been treated with adjuvant chemotherapy, the risk reduction was not significantly different between those with ER-negative tumors and those with ER-positive tumors (40 and 33% respectively). In contrast, among patients older than 50 years, the risk reduction was nearly double for those with ER-negative tumors compared with those with ER-positive tumors, 30 vs 18% (Early Breast Cancer Trialists’ Collaborative Group 1998b).

**Choice of chemotherapy agents**

**CMF**

One of the earliest trials demonstrating improved survival rates with the use of adjuvant chemotherapy was conducted as a cooperative study of the NSABP, ECOG and Central Oncology Group (Fisher et al. 1975). Patients with node-positive disease underwent mastectomy followed by 2 years of treatment with either placebo or mephalan. Improvements in both DFS and recurrence rates were statistically significant for those treated with chemotherapy, $P = 0.02$ and $P = 0.01$ respectively, vs placebo. The NSABP B-13 study then compared 1 year of adjuvant MF with placebo after surgery in women with ER-negative breast cancer (Fisher et al. 1989, 1996b). The women who received MF achieved superior DFS and OS compared with women who received placebo. The NSABP subsequently evaluated the effect of adding cyclophosphamide to MF (i.e. CMF) in the B-19 study. ER-negative patients underwent 6 months of treatment with either CMF or MF after surgery, DFS rates were statistically significantly higher for those taking CMF, 82 vs 73%, $P < 0.001$ (Fisher et al. 1996b). However, when the data were evaluated by age, only those women younger than 50 benefited from the addition of cyclophosphamide.

The landmark Milan study evaluating the effect of 1 year of adjuvant CMF vs no chemotherapy in 391 women with node-positive disease demonstrated a significant reduction in recurrence among those who received chemotherapy (Bonadonna et al. 1976). After 20 years of follow-up, the number of women alive and free from recurrence is still significantly higher than it is among those receiving no chemotherapy, 36 vs 27% respectively (Bonadonna et al. 1995). A subsequent study comparing 12 and six cycles of CMF failed to show the benefit of longer therapy and, therefore, six cycles of CMF has become the standard schedule for this adjuvant regimen.
**Anthrapycines**

On the basis of the superiority of anthracycline-containing regimens in the metastatic setting (A’Hern et al. 1993, Fossati et al. 1998) both doxorubicin and epirubicin have been studied extensively in the adjuvant setting in comparison with standard CMF regimens. The 1998 worldwide overview (Early Breast Cancer Trialists’ Collaborative Group 1998b), included 11 trials that directly compared an anthracycline regimen with CMF. Eight of the 11 trials in this analysis involved a three-drug regimen such as fluorouracil, epirubicin and cyclophosphamide (FEC) or fluorouracil, doxorubicin and cyclophosphamide (FAC) and 70% of the patients accrued were younger than 50 years old. The proportional reductions in DFS and OS rates for those taking an anthracycline were 12 and 11% respectively, with an absolute benefit of 3.2 and 2.7% respectively. The three trials that used a two-drug (doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) combination included more than 50% of the patients in this analysis and had a disproportionate influence on the overall results. Because these three trials showed, at best, the equivalence of AC and EC to CMF, their results have probably diluted the magnitude of the benefits observed with the three-drug combinations (FAC and FEC). Several additional trials have been presented since the 1998 overview that support the benefit of three-drug anthracycline regimens. The NSABP B-23 compared four cycles of AC with six cycles of CMF and demonstrated the equivalence of these two regimens in node-negative, ER-negative disease (Fisher et al. 2001c). The Intergroup 0102 study showed that six cycles of CAF compared with CMF in patients with node-negative disease achieved a 3% absolute improvement in 5-year DFS rates (Hutchins et al. 1998). The Danish-Swedish Cooperative Group compared i.v. CMF, which is generally thought to be superior to the classic Bonadonna CMF regimen (with oral cyclophosphamide), with CEF (Mouridsen et al. 1999). The anthracycline regimen appeared to result in an improved outcome, but this benefit was limited to women with high-risk, node-negative disease and was not seen in the node-positive cohorts. A study from Belgium randomized patients to treatment with classic CMF, low-dose EC (60 mg/m² of epirubicin) or full-dose EC (100 mg/m² of epirubicin). The study found no difference between full-dose EC and CMF, but full-dose EC was found to be superior to low-dose EC in both DFS and OS rates (Piccart et al. 2001). The recently updated Oxford Overview 2000 includes a total of 15 studies comparing anthracyclines with CMF and continues to demonstrate a small but real benefit of three-drug anthracycline regimens compared with CMF (Early Breast Cancer Trialists’ Collaborative Group 2000).

The optimal anthracycline combination and duration of treatment is not known. There has never been a direct comparison of AC/EC and FAC/FEC. However, because use of four cycles of AC or EC has not demonstrated superiority over CMF but the use of six cycles of FAC/FEC has, it is reasonable to offer a six-cycle course of FAC or FEC when prescribing an anthracycline regimen. For node-negative patients, it is acceptable to offer AC × 4 in the adjuvant setting. Whether the apparent success of six cycles of FAC or FEC compared with four cycles of AC or EC is due to the longer duration of chemotherapy or the addition of fluorouracil has yet to be clarified.

The potential long-term side-effects of cardiac dysfunction and leukemia must be taken into account when selecting an anthracycline-based adjuvant chemotherapy regimen. Anthracyclines exert a direct toxic effect on the myocardium, leading to cardiomyopathy in some patients. The risk of developing anthracycline-induced cardiomyopathy depends on the cumulative dose of anthracycline, infusion rate, pre-existing cardiac risk factors and previous radiation therapy to the mediastinum (Buzdar et al. 1989, Hortobagyi et al. 1989, Valagussa et al. 1994, Shapiro et al. 1998, Singal & Iliskovic 1998, Zambetti et al. 2001). Limiting the cumulative dose of epirubicin to 600–720 mg/m² and doxorubicin to 250–300 mg/m² and prolonging the infusion times to 48–96 h reduces the risk of congestive heart failure. The incidence of myelodysplasia and secondary leukemias is increased among patients given CMF and anthracycline-based regimens and correlates with higher cumulative doses of the alkylating agent cyclophosphamide and the use of irradiation (Curtis et al. 1992, Tallman et al. 1995, Diamandidou et al. 1996, Smith et al. 2001). With the more standard doses and schedules of adjuvant regimens, the risk of developing leukemia is approximately 1.5%.

Controversy exists as to whether patients whose tumors overexpress the HER-2/neu oncogene may preferentially benefit from anthracycline regimens instead of CMF regimens. Since the first report of a clear inverse correlation between HER-2/neu overexpression and survival was published (Slamon et al. 1987), research efforts have focused on determining which cytotoxic agents may benefit these patients. Retrospective analyses of three randomized adjuvant trials, including a doxorubicin-containing treatment arm, have concluded that patients with HER-2/neu overexpression derive more benefit from doxorubicin than do patients with HER-2/neu-negative disease (Paik et al. 1998, Ravdin et al. 1998, Thor et al. 1998). However, these analyses are replete with flaws, making these conclusions suspect. The immunohistochemical analysis of the archived tissues varied tremendously between studies and is known to be associated with substantial interobserver variability. Different antibodies were used and the threshold for scoring samples as positive varied widely among the studies. One study considered 1% staining as positive, whereas another considered 50% to be their threshold. In addition, in only one study did the treatment arms differ solely by the presence or absence of doxorubicin. One could easily infer that the cyclophosphamide or fluorouracil, for instance, was responsible for the improved outcome among HER-2/neu...
patients. Lastly, because only 20–30% of breast cancers over-express the HER-2/neu oncogene, very small numbers of patients were evaluated in these studies. Large prospective studies are needed to answer the question of which, if any, cytotoxic agents will confer a preferential survival benefit to this patient population. For now, HER-2/neu status should not affect the choice of an adjuvant therapy regimen.

Currently available data indicate a consistent, statistically significant benefit from the use of anthracyclines as part of three-drug regimens compared with CMF in the adjuvant setting. However, the small but real risks of leukemia and cardiac dysfunction should be taken into account when selecting an adjuvant regimen, particularly for those in whom adjuvant chemotherapy results in a small absolute benefit.

Taxanes

In the metastatic setting, both paclitaxel and docetaxel have demonstrated impressive efficacy (Holmes et al. 1991, Reichman et al. 1993, Chan et al. 1999, Sjostrom et al. 1999), with docetaxel even resulting in a survival benefit in a phase III study (Nabholtz et al. 1999). In an attempt to further improve the survival benefit resulting from anthracycline-containing adjuvant chemotherapy regimens, both taxanes are being studied in many ongoing clinical trials. Data are now available from four large randomized adjuvant trials that compared an anthracycline-based regimen with a regimen including a taxane, but these data yield conflicting results.

The Cancer and Leukemia Group B (CALGB) 9344 study was the first adjuvant taxane study reported. It compared four cycles of AC with four cycles of AC followed by four cycles of 175 mg/m² of paclitaxel. At 18 months of follow-up, the paclitaxel-treated patients had a 22% proportional reduction and 4% absolute improvement in DFS compared with the patients given AC alone (Henderson et al. 1998). When the data were updated at 30 months of follow-up and presented to the US Food and Drug Administration, identical benefits were seen, which led to the approval of paclitaxel for the adjuvant therapy of node-positive breast cancer. A second prospective randomized adjuvant trial, conducted at The University of Texas MD Anderson Cancer Center, compared eight cycles of FAC with four cycles of paclitaxel (250 mg/m² over 24 h) followed by four cycles of FAC. At 43 months of follow-up, there was a non-significant trend toward reduced recurrence in patients treated with paclitaxel (Thomas et al. 2000). At the National Institutes of Health (NIH) Consensus Development Conference in 2000, data from these two studies, as well as early data from the NSABP B-28 trial, were reviewed to assess the potential effect of adjuvant paclitaxel therapy. The NSABP B-28 treatment schema was virtually identical to that of the CALGB 9344 trial, except that in the former trial patients received concomitant tamoxifen and the paclitaxel dose was 225 mg/m². With this longer follow-up, the CALGB 9344 data demonstrated significantly less reduction in recurrence for paclitaxel (13 vs the 22% reduction seen at 30 months of follow-up) and a non-significant improvement in OS. The NSABP B-28 study failed to show any benefit to the use of paclitaxel in the overall group. In both studies, only the ER-negative cohort (in an unplanned subset analysis) appeared to derive benefit from the sequential use of paclitaxel.

On the basis of the data from these three trials, the NIH Consensus Development Panel believed that firm conclusions could not be reached about the effect of taxanes on DFS or OS rates. With so few patients with node-negative tumors included in these studies (only the MD Anderson study included such patients), the NIH panel recommended that these patients be treated with adjuvant taxanes only in the context of a clinical trial (National Institutes of Health Consensus Development Panel 2001). Since the NIH Consensus statement was published, the MD Anderson Cancer Center trial results have been updated and published, and its data continue to show a trend in favor of the use of sequential paclitaxel with FAC, although the trend does not reach the level of statistical significance (Buzdar et al. 2002). Another interesting observation can be made on the basis of the MD Anderson trial: the DFS curves of paclitaxel and control treatment groups start to separate within the first 6 months of follow-up for patients with ER-negative tumors, whereas for those with ER-positive tumors, no separation in the DFS curves becomes evident until after the first 3 years of follow-up.

The results of the first adjuvant trial incorporating docetaxel, the Breast Cancer International Research Group (BCIRG) 001 trial, have recently been reported (Nabholtz et al. 2002). This trial compared six cycles of FAC with six cycles of docetaxel, doxorubicin and cyclophosphamide (TAC). Unlike the CALGB and NSABP studies, in which the treatment groups differed both in the number of chemotherapy cycles and in the addition of paclitaxel, the BCIRG trial treated all patients with six cycles of chemotherapy, differing only in the substitution of docetaxel for fluorouracil. At 33 months of follow-up, the TAC-treated patients experienced a 32% reduction in risk of recurrence and an absolute 8% improvement in DFS. The benefit was more marked for those with one to three positive nodes than in those with four or more involved nodes. It is notable that the benefits of TAC were seen in patients with both ER-positive and -negative tumors (Table 2), with the benefit becoming apparent earlier for the patients in the ER-negative group. Longer follow-up is necessary to determine the ultimate effect of this docetaxel combination regimen on survival in early breast cancer.

Until more mature data become available from ongoing adjuvant trials incorporating taxanes, the role of paclitaxel and docetaxel remains unclear. On the basis of the impressive...
results of the taxanes in the setting of metastatic disease, the high pathological complete response (pCR) rates of the taxanes in the neoadjuvant setting, and the recent BCIRG 001 trial, it is likely that one or both of the taxanes will affect the survival of patients with early breast cancer. Whether taxanes are most effective given simultaneously with older agents or administered sequentially, before or after standard combinations, remains to be clarified in the numerous ongoing studies.

Trastuzumab

The HER-2/neu oncoprotein is a tyrosine kinase transmembrane growth factor receptor that is overexpressed on 20–30% of breast cancers and is associated with an adverse outcome for most patients (Slamon et al. 1987). It correlates with other poor prognostic features such as ER-negativity, high proliferative rate, and high tumor grade. Trastuzumab, a monoclonal antibody directed against the HER-2/neu receptor, as Herceptin, has been shown to increase the survival of patients with early breast cancer. Whether taxanes are most effective given simultaneously with older agents or administered sequentially, before or after standard combinations, remains to be clarified in the numerous ongoing studies.

**Table 2** Comparison of results from adjuvant taxane trials

<table>
<thead>
<tr>
<th>CALGB</th>
<th>NSABP B-28</th>
<th>MDACC</th>
<th>BCIRG 001</th>
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<tr>
<td>No. of patients</td>
<td>3170</td>
<td>3060</td>
<td>524</td>
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<tr>
<td>Median follow-up (months)</td>
<td>52</td>
<td>34</td>
<td>60</td>
</tr>
<tr>
<td>Absolute benefit in DFS (%)</td>
<td>4*</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Relative reduction in recurrence (%)</td>
<td>13*</td>
<td>7</td>
<td>34</td>
</tr>
</tbody>
</table>

*P = 0.05. MDACC, MD Anderson Cancer Center.

Duration of adjuvant chemotherapy

The initial studies evaluating the potential benefit of adjuvant chemotherapy used a short perioperative course of chemotherapy that resulted in minimal benefits (Nissen-Meyer et al. 1971, Fisher et al. 1977, Kjellgren et al. 1989, Ludwig Breast Cancer Study Group 1990). A subsequent study of 222 women with node-positive disease compared 12 weeks of cyclophosphamide, methotrexate, fluorouracil, vincristine and prednisone (CMFVP) followed by doxorubicin and tamoxifen with 36 weeks of CMFVP. The resulting 3-year relapse-free survival rates were 55 and 64% respectively, demonstrating the inferiority of the shorter regimen (Levine et al. 1990). Similarly, a study of 1554 premenopausal patients with node-positive disease evaluated treatment duration with a 2 × 2 factorial study design. Patients were randomized to take CMF for three or six cycles and were then further randomized either to receive no additional therapy or to be given single courses of CMF at months 6, 9 and 12. Those treated with CMF for only three cycles demonstrated a poorer 5-year DFS rate (53%) than did those in the other three treatment groups, all of whom fared equally well (58%) (International Breast Cancer Study Group 1996). To address the issue of whether considerably longer durations may be beneficial, 2 years of CMFVP therapy was compared with 1 year of therapy in a prospective study of 455 women with node-positive, ER-negative tumors. The report at 8 years of follow-up showed equivalent 5 year survival rates for the two treatment groups, 57 and 62% respectively (Rivkin 1993). Intermediate treatment durations were studied in Milan among premenopausal patients with node-positive disease who were randomized to treatment with CMF for either six or 12 cycles. The relapse-free survival rate was not significantly different between the treatment arms (Tancini et al. 1979, 1983).

Based on these data and the meta-analysis performed in the Oxford Overview (Early Breast Cancer Trials’ Collaborative Group 1998b), the current optimal adjuvant chemotherapy duration is 3–6 months of the commonly used regimens, such as AC with or without fluorouracil or CMF. However, ongoing prospective adjuvant trials incorporating sequential chemotherapy combinations with taxanes require up to 6 months of therapy. Therefore, these recommendations may change as data from ongoing trials accumulate.

Timing of adjuvant chemotherapy

Adjuvant chemotherapy has traditionally been administered exclusively in the postoperative setting. However, numerous studies have evaluated its use preoperatively. The potential benefits of this neoadjuvant chemotherapy include downstaging the primary tumor to allow for breast-conserving surgery and assessing a tumor’s in vivo sensitivity to individual chemotherapeutic regimens. The largest study evaluating the
Table 3 Ongoing trastuzumab (Hercep tin) adjuvant trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment schema</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B–31</td>
<td>AC × 4 paclitaxel q 3 weeks × 4</td>
</tr>
<tr>
<td></td>
<td>paclitaxel q 3 weeks × 4 + weekly Herceptin × 1 year</td>
</tr>
<tr>
<td>Intergroup N9831</td>
<td>AC × 4 paclitaxel q weeks × 12</td>
</tr>
<tr>
<td></td>
<td>paclitaxel q weeks × 12 followed by weekly</td>
</tr>
<tr>
<td></td>
<td>Herceptin × 1 year</td>
</tr>
<tr>
<td></td>
<td>paclitaxel q weeks × 12 + weekly Herceptin × 1 year</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>Randomize AC × 4 → docetaxel q 3 weeks × 4</td>
</tr>
<tr>
<td></td>
<td>AC × 4 → docetaxel q 3 weeks × 4 +</td>
</tr>
<tr>
<td></td>
<td>Herceptin weekly × 1 year</td>
</tr>
<tr>
<td></td>
<td>docetaxel/carboplatin q 3 weeks × 6 +</td>
</tr>
<tr>
<td></td>
<td>Herceptin weekly × 1 year</td>
</tr>
<tr>
<td>HERA</td>
<td>Primary therapy Herceptin q 3 weeks × 1 year</td>
</tr>
<tr>
<td></td>
<td>Herceptin q 3 weeks × 2 years</td>
</tr>
<tr>
<td></td>
<td>observation</td>
</tr>
</tbody>
</table>

HERA, herceptin adjuvant; q, every.

effect of neoadjuvant chemotherapy was the NSABP B-18 trial (Fisher et al. 1997a, Wolmark et al. 2001). In this study, 1523 women were randomized to treatment with four cycles of AC either before or after surgical resection. The timing of chemotherapy did not affect the DFS or OS rates for the entire cohort, although more patients who received preoperative therapy were able to undergo breast-conserving surgery rather than mastectomy than were those treated postoperatively. However, an important finding in this study was the clear correlation of pCR in the breast (i.e. absence of invasive cancer cells) with survival (Fisher et al. 1998). The pCR rate has become one of the most important trial end points in assessing the efficacy of new adjuvant chemotherapy regimens.

A similar association between pathological response and survival was shown when axillary lymph nodes were found to be clear of cancer cells after neoadjuvant FAC chemotherapy at the MD Anderson Cancer Center (Feldman et al. 1986, Kuerer et al. 1999). Published studies of anthracycline-based preoperative chemotherapy demonstrated pCR rates of up to 17% (Fisher et al. 1997a, Buzdar et al. 1999). Results of several recently reported studies of the sequential use of anthracycline-based regimens and taxanes compared with anthracycline regimens alone have shown significantly higher pCR rates ranging from 25 to 34% (National Surgical Adjuvant Breast and Bowel Project 2001, Green et al. 2002, Smith et al. 2002). Longer follow-up is necessary to determine whether these high pCR rates seen from the sequential use of taxanes in the preoperative setting will translate to a favorable impact on survival rates.

Dose intensity

When the initial worldwide adjuvant overviews demonstrated that adjuvant therapy provided a survival benefit to patients with early breast cancer, the question of the importance of dose intensity arose as well. If chemotherapy improved survival, would higher doses achieve even longer survival? Bonadonna & Valagussa (1981) attempted to answer the question for CMF regimens in a retrospective analysis of two CMF trials to determine whether patients who received substantial dose reductions experienced the same survival rate as those who received standard doses of CMF. One study compared 12 cycles of CMF with no adjuvant therapy and the other compared six cycles of CMF with 12 cycles. There was a clear correlation between the percentage of the planned dose that was administered and survival. Patients given at least 85% of the planned doses of CMF had much better survival rates than did those given lower doses. This analysis demonstrated that the dose of chemotherapy used is indeed important to the survival rate in the adjuvant setting. On the basis of these data, other studies sought to assess the value of increasing the dose of doxorubicin, epirubicin or cyclophosphamide in the adjuvant setting. The CALGB conducted a
prospective, randomized clinical trial to compare the dose density and intensity of CAF regimens (Wood et al. 1994). Women were randomized to treatment with CAF at doses (in mg/m²) of 400/40/400 every 4 weeks for six cycles, 600/60/600 every 4 weeks for four cycles, or 300/30/300 every 6 weeks for six cycles. Patients in the first two groups fared equally well, whereas those in the third group with its lower total dose and longer treatment intervals, demonstrated significantly inferior survival. This study helped to clarify the importance of administering adjuvant chemotherapy at regular 3- to 4-week intervals to achieve maximum benefit. The CALGB 9344 study, mentioned earlier, tested both the dose intensity of doxorubicin and the addition of sequential paclitaxel in a $3 \times 2$ factorial design (Henderson et al. 1998). Patients were randomized to treatment with four cycles of AC at one of three doses of doxorubicin (60, 75 or 90 mg/m²) before treatment with either four cycles of paclitaxel or no further therapy. The efficacy was the same regardless of the dose of doxorubicin received. The results of these two studies, taken together, show that the dose escalation of doxorubicin to a specific threshold (i.e. 40–60 mg/m²), but not beyond, is necessary to confer a survival advantage. The French Adjuvant Study Group examined the effect of two different doses of epirubicin in the FEC regimen for patients with node-positive breast cancer. Five hundred and sixty-five women were randomized to receive six cycles of FEC with either 50 or 100 mg/m² of epirubicin. At 5 years of follow-up (French Adjuvant Study Group 2001), both DFS (54 vs 66%, $P = 0.03$) and OS (65 vs 77%, $P = 0.007$) were superior among patients who received the higher dose of epirubicin. Therefore, the higher dose of epirubicin should be used in adjuvant regimens.

In the 1990s, the NSABP recognized that there was a paucity of prospective data in the 1990s on the role of dose density and intensity in the adjuvant setting and conducted two trials to address this issue with respect to cyclophosphamide. NSABP B-22 and B-25 compared the intensification of cyclophosphamide doses in conjunction with a standard doxorubicin dose. In the B-22 trial, 2305 patients were randomized to one of three AC treatment groups: group 1 was treated with the standard doses of AC (60 and 600 mg/m²) for four cycles; group 2 was treated with 60 mg/m² of doxorubicin for four cycles and 1200 mg/m² of cyclophosphamide for cycles 1 and 2 only; and group 3 was treated with 60 mg/m² of doxorubicin and 1200 mg/m² of intensive cyclophosphamide for all four cycles. The 5-year DFS and OS rates were not significantly different between the treatment groups but toxicities were clearly higher in groups 2 and 3 (Fisher et al. 1997b). In group 3, 21% of patients experienced grade 4 toxicities, including three cases of leukemia, in contrast to one case of leukemia in the standard AC group.

There was no substantive benefit to escalating the cyclophosphamide dose in the B-22 trial, but it was postulated that perhaps it was necessary to intensify the dose further to confer a survival benefit. Hence, the B-25 trial was initiated to test this hypothesis. Again, three treatment groups compared AC with intensified cyclophosphamide doses in 2548 patients with node-positive disease. Group 1 was treated with four cycles of AC (60/1200 mg/m²); group 2 was treated with four cycles of 60 mg/m² of doxorubicin and 2400 mg/m² of cyclophosphamide for the first two cycles only; and group 3 was treated with four courses of AC (60/2400 mg/m²). Similar to the findings in the B-22 trial, there were no significant differences in DFS or OS rates of any treatment group (Fisher et al. 1999). The toxicities in this study were far higher than in B-22: 49% of patients in group 3 experienced grade 4 toxicities, including 44% of whom developed grade 4 sepsis. Fifteen patients in this study developed acute myeloid leukemia, as would be expected with high doses of an alkylating agent. Thus, these two studies provided no evidence that intensifying the dose of cyclophosphamide beyond the standard dose of 600 mg/m² confers a survival benefit.

High dose chemotherapy with stem cell rescue

The unfavorable outcome for women with high-risk, node-positive breast cancer prompted studies evaluating various high-dose chemotherapy regimens with stem cell support. There are data from six randomized trials that prospectively compared the efficacy of high-dose chemotherapy with that of more standard regimens. Unfortunately, only three of the studies included more than 100 patients and one study of the six was discredited because of substantial scientific misconduct discovered in a rigorous audit and will not be discussed further (Bezwoda 1999, Weiss et al. 2000).

The largest of these trials is a Dutch study in which 885 patients were treated with four cycles of FEC and then randomized to treatment with either an additional cycle of FEC or high-dose therapy with cyclophosphamide, thiopeta and carboplatin with stem cell support. There were four deaths from toxicity in the high-dose group compared with one in the standard FEC group. At a planned interim evaluation of the first 284 patients, there was a highly statistically significant improvement in DFS and OS rates, 15 and 10% respectively (Rodenhuis et al. 2000). However, an evaluation of the entire population by intent-to-treat did not demonstrate significant differences between the two groups.

The CALGB study compared intermediate-dose and high-dose chemotherapy rather than high-dose chemotherapy and standard chemotherapy (Peters et al. 1999). In this study, 785 patients with ten or more positive axillary lymph nodes were treated with four cycles of CAF followed by intermediate or high doses of cyclophosphamide, Carmustine and cisplatin. The survival rates were equivalent (approximately 70%). Although this was not a pure evaluation of high-dose
vs standard chemotherapy, the impressive survival rates for this high-risk patient population are intriguing.

These data indicate that dose intensity to a specific threshold is essential, but there is no clear benefit to high-dose therapy in the adjuvant setting outside of a clinical trial. Long-term data from these and ongoing studies are awaited.

Conclusions

Adjuvant hormone therapy with tamoxifen has consistently been found to improve survival rates for women with invasive breast cancer and to reduce the incidence of new primary tumors. These benefits are confined to the subgroup of patients with ER-positive tumors. No benefit is observed among patients with ER-negative tumors. The recent data comparing anastrozole and tamoxifen in the adjuvant setting are promising but require longer follow-up and corroborative data from ongoing hormone therapy trials before anastrozole can uniformly replace tamoxifen. Combination hormone therapy with other hormone agents may be better, but is currently under active investigation.

Each Oxford Overview has repeatedly demonstrated substantial, durable benefits of adjuvant chemotherapy in all subgroups of patients with invasive breast cancer, irrespective of menopausal status, axillary nodal status, age or ER status. The absolute benefit is clearly higher for those with involved axillary lymph nodes. The benefit for each patient must be weighed against the potential adverse effects of chemotherapy. The only subsets of patients for whom the risks of chemotherapy often outweigh the benefits include those with tumors smaller than 1 cm and negative lymph nodes, and those with small tumors (<3 cm) with favorable histological types, such as tubular, papillary, mucinous and adenoid cystic carcinomas. The current data on the incorporation of taxanes are promising but not yet compelling enough to warrant the inclusion of taxanes in regimens for all patients. It is reasonable to include paclitaxel or docetaxel for patients with node-positive disease. Numerous trials are currently assessing the schedule and sequence of both taxanes in the adjuvant setting and should help clarify their importance and impact on survival. For now, the current available data indicate that effective regimens for node-positive patients include six cycles of FAC or FEC, or four cycles of FAC or FEC or AC followed by four cycles of a taxane, or six cycles of TAC. For node-negative patients, four cycles of AC, six cycles of FAC or FEC, and six cycles of CMF are reasonable options.

High-dose therapy with stem cell support has not demonstrated a consistent, favorable impact on survival and should not be routinely used for patients with early-stage breast cancer outside the context of a clinical trial. The success of trastuzumab in the metastatic setting has generated great enthusiasm for its potential use in the adjuvant setting for patients whose tumors overexpress the HER-2/neu oncogene. However, the small but real incidence of cardiomyopathy associated with trastuzumab must be factored into the risk-to-benefit ratio of trastuzumab combination chemotherapy, particularly for women with early-stage tumors. Until results of the ongoing trials have been reported, the use of trastuzumab should remain investigational in the adjuvant setting.

Current breast cancer research is focused on the biological features of an individual tumor and will, we hope, lead to means of tailoring therapy appropriately to improve the therapeutic indices for adjuvant therapy regimens.

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