Future directions in the adjuvant treatment of breast cancer:
The role of trastuzumab

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Summary

Current evidence shows that adjuvant cytotoxic or hormonal therapy increases the disease-free and overall survival of patients. The analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that anthracycline/cyclophosphamide (AC)-containing regimens are more effective than those without AC, providing an 11% greater reduction in the risk of death compared with non-AC-containing regimens. In addition, paclitaxel and docetaxel have significant anti-tumor activity in previously treated patients and sequential treatment with paclitaxel may further reduce the risk of recurrence and improve survival. Tamoxifen is effective in reducing the risk of recurrence and death in patients with estrogen receptor (ER)-positive tumors. The addition of tamoxifen to combination chemotherapy in patients with ER-positive tumors further reduces the risk of recurrence and improves survival. Debate on the effectiveness of tamoxifen in HER2-positive patients is currently underway. A number of trials are in progress or planned to investigate the use of the anti-HER2 monoclonal antibody trastuzumab (Herceptin) in the adjuvant setting. These include a National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant trial (AC -> paclitaxel vs. AC -> paclitaxel + trastuzumab) and an Intergroup study (AC -> paclitaxel vs. AC -> paclitaxel + trastuzumab vs. AC -> paclitaxel + trastuzumab). Results from these trials will determine whether this novel therapy has a survival benefit in early breast cancer.

Key words: adjuvant breast cancer, anthracyclines, CMF, HER2, Herceptin, taxanes, trastuzumab

Introduction

There has been significant progress in systemic adjuvant therapy of early breast cancer over the past 10–20 years. Evidence shows that the addition of adjuvant hormonal and chemotherapy increases disease-free and overall survival for many women.

The key sources of evidence at present are the reviews by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [1–3]. These provide 10-year follow-up data from a large group of randomized trials, providing perhaps one of the most powerful collections of data available in medicine at this time.

This report provides an overview of the EBCTCG's extensive analysis of trial data, together with a discussion of the recent advances in and current recommendations for adjuvant care of breast cancer. The potential implications of new biologic agents, such as the anti-HER2 monoclonal antibody trastuzumab (Herceptin), for the future of adjuvant therapy are also discussed.

Adjuvant chemotherapy for breast cancer (EBCTCG overview)

The EBCTCG reviewed a total of 47 trials in over 18,000 women, examining the role of chemotherapy vs. no chemotherapy, together with a further 11 trials examining 6000 patients entered into trials of anthracyclines vs. non-anthracycline chemotherapy. The key findings from this review of adjuvant chemotherapy are summarized in Table I.

Overall, chemotherapy provided a 23% proportional decrease in recurrence rate and a 15% decrease in all-cause mortality in comparison to no chemotherapy. This resulted in statistically significant absolute decreases in recurrence and death for all age groups studied up to 69 years. There were only small numbers of patients studied over the age of 69 years, making comparisons in this group difficult.

Risk reductions for axillary lymph node-positive and -negative women were proportionally the same. Absolute

<table>
<thead>
<tr>
<th>Age and Nodal Status</th>
<th>Absolute benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence (%)</td>
<td>Mortality (%)</td>
</tr>
<tr>
<td>&lt; 50 years of age</td>
<td></td>
</tr>
<tr>
<td>Node negative</td>
<td>10</td>
</tr>
<tr>
<td>Node positive</td>
<td>15</td>
</tr>
<tr>
<td>50–69 years of age</td>
<td></td>
</tr>
<tr>
<td>Node negative</td>
<td>6</td>
</tr>
<tr>
<td>Node positive</td>
<td>5</td>
</tr>
</tbody>
</table>
risk reductions in recurrence and mortality are shown in Table 1. These were greatest in node-positive patients < 50 years of age with recurrences in recurrence and mortality of 15% and 12%, respectively. For women over the age of 50 years risk reductions were less, with an absolute gain in survival of 2%-6%. It becomes a value judgement in this group of women as to whether such benefits are worthwhile.

Significant benefit continued even after five years for those women aged < 50 years who had chemotherapy compared with controls in both recurrence rate and overall survival. The mortality benefits after five years were also seen in the 50-69-year age group. Thus for controls and treated women surviving to five years, prognosis remained better for those who had been treated with chemotherapy (Table 2).

Are anthracyclines more effective as adjuvant treatment?

In the EBCTCG overview, anthracycline-containing chemotherapy gave statistically superior recurrence-free and overall survival compared with non-anthracycline regimens, although the magnitude of the benefit was small (absolute survival improvement of 2%-3%). In the 10 randomized trials included in the overview, five showed increased disease-free survival and three showed increased overall survival. None showed inferior results for anthracyclines. Toxicity was somewhat greater for anthracycline-containing combinations.

In a more recent trial, an anthracycline regime was compared with classic CMF (cyclophosphamide-methotrexate-5-fluorouracil) in pre-menopausal women [4]. There was a statistically significant absolute survival increase of 7% at five years for those who received anthracyclines. However, in the anthracycline arm, 50% had grade 2 or more nausea and vomiting compared with 25% in the CMF arm. Similarly, stomatitis was 45% vs. 25% and alopecia 97% vs. 40%, respectively. There was no difference in the myelotoxicity between the two arms. Cardiotoxicity is a potential problem, but this is rare when recommended cumulative doses are not exceeded. It did not occur in any of 351 patients given anthracycline in this trial. Quality of life scores were lower during chemotherapy for the anthracyline group, but were the same by six months after chemotherapy.

The role of taxanes in adjuvant care

In a recent trial involving 3170 women, half of whom were randomized to receive four cycles of paclitaxel given three times weekly after completing four cycles of adjuvant doxorubicin and cyclophosphamide, use of paclitaxel reduced the recurrence rate by 22% and the death rate by 26% at 18 months compared to doxorubicin-cyclophosphamide alone [5] (Table 3). At a three-year analysis the results were unchanged. These results sound more impressive than they really are: the absolute reduction in mortality is so far only 2% ($P = 0.0390$), but this may enlarge or decrease with further follow-up. Further trials using both adjuvant paclitaxel and docetaxel await completion and analysis. New studies will examine the role of sequence and dose densification of the taxanes as well as their role in node-negative, high-risk tumors. Anthracyclines followed by paclitaxel has become a standard treatment for node-positive disease in the USA but not yet in Europe.

### Table 2. Continued benefit from adjuvant chemotherapy with time.

<table>
<thead>
<tr>
<th>Time from randomization (years)</th>
<th>Recurrence (%)</th>
<th>Mortality (any cause)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5</td>
<td></td>
<td></td>
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</tbody>
</table>

Table 2. Proportional risk reduction compared with control.

<table>
<thead>
<tr>
<th>Disease-free survival</th>
<th>AC (%)</th>
<th>AC -&gt; paclitaxel (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3170 node-positive patients (62% pre-menopausal). AC x 4 -&gt; paclitaxel 175 mg/m² every 3 weeks x 4. Eighteen-month analysis. Grade 3 toxicity for paclitaxel: 25% WBC, 5% neuropathy, 5% pain.</td>
<td></td>
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</tbody>
</table>

### Table 3. Addition of paclitaxel to AC significantly improves disease-free and overall survival in the adjuvant setting. (Adapted with permission from Henderson et al. [5]).

**Overview of tamoxifen in adjuvant breast cancer**

In the 1998 overview [2], individual patient data were reviewed from trials of tamoxifen vs. no tamoxifen started before 1990, with an average follow-up of 10 years. Individual patient data were collected for 37,000 women in 55 trials, nearly 8000 of whom had estrogen receptor (ER)-poor tumors (<10 fmol/mg). This group did not benefit from tamoxifen and were excluded from further analysis. Of the remaining women, approximately 18,000 had ER-positive tumors and 12,000 had unknown ER status, of whom two-thirds were assumed to have been ER positive. This large data set allows statistically powerful conclusions on many aspects regarding adjuvant tamoxifen usage.

The influence of duration of tamoxifen use is shown in Table 4. This shows that five years' tamoxifen treatment is better than a shorter duration of treatment; the risk reduction in mortality at one, two and five years for ER-positive women was 14%, 18% and 28%, respectively, and this difference was highly significant, $2P < 0.00001$. The proportional risk reductions for recurrence and mortality were approximately the same for node-positive and -negative patients. The absolute risk reduction was greater for node-positive than node-negative patients in
that their overall risk of recurrence and death is higher. The absolute reduction in mortality with five years of tamoxifen was 11% for node-positive and 6% for node-negative patients.

The benefit for mortality and recurrence reduction continued into the second five years after randomization. ER-positive women who had a 50% reduction in their rate of relapse in the first five years after randomization continued to have a one-third reduction in relapse in the second five years compared with control. Interestingly, the proportional mortality reductions for the second five years were the same as for the first five years, showing prolonged continued benefit after discontinuation of tamoxifen.

**Tamoxifen in HER2-positive cancers**

There is current concern about the role of adjuvant tamoxifen in patients with HER2-positive cancers. In a 20-year update of the Naples GUN trial which randomized women to two years’ tamoxifen or no treatment, HER2 status was determined retrospectively in 245 of 433 patients [6]. Overall, at a median follow-up of 14 years, tamoxifen improved disease-free and overall survival, but only in HER2-negative patients in whom there was a 19% decrease in expected death rate in patients on tamoxifen. In stark contrast there was a 57% increase in mortality for HER2-positive patients on tamoxifen. In a multivariate analysis, HER2 positivity independently predicted for tamoxifen failure.

In a large Scandinavian trial of two vs. five years of tamoxifen in ER-positive, early breast cancer patients, HER2 status was measured in 449 women in a post hoc analysis [7]. Results showed 13% of those who were disease free two years after surgery had HER2-gene amplification or protein overexpression on examination of their tumors. HER2-negative patients had a 0.65 relative risk of recurrence with five vs. two years of tamoxifen. HER2-positive patients, in contrast, had a suggested increase in their relative risk, 1.9 (confidence interval (CI): 0.54–6.6) on tamoxifen, although this was not statistically significant. This suggests that prolonged tamoxifen therapy may not be beneficial in patients with ER-positive tumors if also HER2 positive.

Contradictory data have been obtained from the CALGB 8541 trial in which tissue from ER-positive women who had received tamoxifen for 10 years was assessed for HER2 status [8]. Results in this relatively small number of patients revealed that the five-year

| Table 4. Effects of tamoxifen duration and ER status on mortality. |
|---------------------------------|-----------------|------------------|
| Duration (years)      | Proportional reduction in mortality (%) |               |
|                      | ER poor | ER unknown | ER positive |
| 1                    | 6  | 10  | 14          |
| 2                    | 17 | 15  | 18          |
| 5                    | -3 | 21  | 28          |

Table 5. Adjuvant tamoxifen in HER2-positive patients. (Adapted with permission from Muss et al. [8])

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>HER2 positive</th>
<th>HER2 negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving tamoxifen</td>
<td>186</td>
<td>555</td>
</tr>
<tr>
<td>Five-year relapse-free survival</td>
<td>68 (37%)</td>
<td>263 (47%)</td>
</tr>
<tr>
<td>with tamoxifen (%)</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>with no tamoxifen (%)</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Reduction in risk of relapse (%)</td>
<td>42</td>
<td>44</td>
</tr>
</tbody>
</table>

CALGB 8541 reanalyzed. No interaction of tamoxifen and HER2 status.

relapse-free survival and reduction in risk of relapse were similar in both HER2-positive and -negative patients (Table 5). Survival curves for HER2 overexpressors were identical to those for HER2-negative patients.

At present, therefore, the role of adjuvant tamoxifen in HER2-positive patients remains uncertain.

**Trastuzumab: A new therapeutic option in adjuvant breast cancer**

Amplification of the HER2 gene confers a poorer outlook for both node-positive and -negative patients with early breast cancer. HER2 status is increasingly being considered as one of a number of prognostic factors in early breast cancer when determining the most appropriate chemotherapy regimen. New biologically targeted therapies are also being investigated in the adjuvant setting. One such novel agent is the anti-HER2 monoclonal antibody, trastuzumab, which has been shown to produce a significant survival benefit in combination with chemotherapy (AC or paclitaxel) in HER2-positive metastatic breast cancer patients when given as first-line treatment [9–11]. Furthermore, trastuzumab is generally well tolerated and non-cross-resistant with chemotherapy agents.

A problem in considering trastuzumab as adjuvant therapy is the unexpected risk of developing cardiac dysfunction, particularly when combined with the anthracycline doxorubicin. This would require careful monitoring in patients with early breast cancer who have potentially curable disease. It has been suggested that the issue of cardiotoxicity could be avoided by simply using trastuzumab with agents other than doxorubicin. Despite this possibility, there are several compelling reasons for using anthracyclines in the adjuvant setting. Firstly, follow-up results from the CALGB 8541 study, examining dose intensification of CAF (cyclophosphamide–doxorubicin–5-FU), have revealed that patients receiving the high and moderate (standard) doses of CAF survive longer than those receiving the low dose [12]. Secondly, examination of patients’ HER2 status within this trial revealed that those with tumors expressing high levels of the HER2 protein had a significantly worse survival if treated with moderate or low-dose intensity CAF chemotherapy, compared with standard dose intensity (Figure 1).
Planned trials with trastuzumab

A number of trials are either planned or underway with trastuzumab in the early breast cancer setting. These are summarized below.

National Surgical Adjuvant Breast and Bowel Project trial

A National Surgical Adjuvant Breast and Bowel Project (NSABP) trial currently underway involves node-positive, HER2-positive patients receiving four courses of AC followed by randomization to receive four courses of paclitaxel vs. the same treatment but with trastuzumab added weekly for one year. A three-week gap exists between patients finishing their course of AC and starting trastuzumab, and patients will undergo extensive cardiac monitoring to avoid the potential risk of cardiotoxicity associated with this combination.

Objectives for the trial include improvement in disease-free and overall survival and also the determination of any major cardiac safety issues. If an incidence of cardiac dysfunction > 5% is observed in the first 1000 patients the trial will be discontinued. Patients will also be stratified according to their prior exposure to tamoxifen. All those who are ER/progesterone receptor (PgR) positive will receive tamoxifen and those who are > 50 years of age have the option of receiving tamoxifen regardless of their ER/PgR status.

Intergroup trial

An Intergroup trial in progress has a very similar design to the NSABP trial as discussed above. The first two arms are identical, although the Intergroup trial includes a third arm in which trastuzumab is given after the four courses of paclitaxel, thereby increasing the period of time between receiving anthracyclines and receiving trastuzumab. This trial has roughly the same entry criteria to the NSABP trial, together with the same degree of cardiac monitoring.

Alternatives to the combination of trastuzumab plus doxorubicin in the adjuvant setting

In an attempt to avoid any potential cardiotoxicity following administration of trastuzumab plus doxorubicin, other therapeutic combinations are being considered. These options include trastuzumab plus CMF, epirubicin, liposomal doxorubicin, taxane–cisplatin (or carboplatin) or taxane–vinorelbine.

Trastuzumab plus CMF

Despite being one of the earliest cytotoxic options for adjuvant therapy in breast cancer, data available suggest that CMF is comparable to the anthracyclines in terms of survival benefit. Indeed, an analysis of 337 patients included in the original Milan trial of classical, dose-intensive CMF (CMF × 12 vs. control) revealed that those who were HER2 positive (16%) had a significant overall survival benefit from CMF compared with the control patients who were HER2 positive (Figure 2) [14, 15]. These observations were important in view of previous data suggesting that adjuvant CMF did not produce any clinical benefit in HER2-positive patients. As this trial demonstrated an appreciable survival benefit from dose-intensive CMF, it can be suggested that other studies having failed to show any benefit may have employed a less-intensive regimen of CMF.

Other agents

The anthracycline epirubicin is a potentially useful drug in the adjuvant setting and is much more widely used in Europe than the USA. Epirubicin is associated with a lower incidence of cardiotoxicity than doxorubicin, and an important German trial is addressing the incidence of cardiac dysfunction following epirubicin–cyclo-
phosphamide–trastuzumab in patients with metastatic disease. Encapsulating the drug doxorubicin in liposomes has been proposed to limit its cardiotoxic effects, although clinical trials with liposomal doxorubicin are not yet advanced enough to make conclusions on its efficacy and safety. Finally, the theoretical advantages of using different schedules of various cytotoxic agents, such as a taxane with cisplatin–carboplatin or a taxane with vinorelbine, is problematic at this time because these are not standard recognized schedules in advanced breast cancer.

Conclusions

Adjuvant chemotherapy improves survival in early breast cancer. In the USA, AC followed by paclitaxel is increasingly favored for high-risk patients. In Europe, FAC/FEC or CMF remain the standard.

The humanized anti-HER2 monoclonal antibody trastuzumab is an attractive drug for adjuvant therapy because of its prolongation of survival in metastatic disease, lack of cross resistance to other agents, and low incidence of toxicity. In order to answer questions relating to the issue of cardiotoxicity following administration of a combination of trastuzumab and doxorubicin, a number of trials are underway in both metastatic patients and in the adjuvant setting. In addition, it is important to consider non-anthracycline combinations. Finally, the important issue of whether trastuzumab may confer a survival benefit to tamoxifen treatment in HER2-positive patients, perhaps reversing the reduction in response previously observed with tamoxifen in a number of trials, is currently being considered.

Note

Professor Smith has reported that he serves on a Roche advisory board for Herceptin.

References


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