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Developments in the systemic therapy of early-stage breast cancer

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ABSTRACT

Breast cancer is a heterogeneous disease classified by variations in gene expression, and as such, concepts regarding treatment recommendations according to molecular classification are being explored. Retrospective data from hypothesis-generating subset analyses of adjuvant clinical trials have shown that patients with lower oestrogen receptor (ER) expression are more likely to benefit from adjuvant chemotherapy compared with patients who have intermediate or high ER expression. In addition, greater benefit is obtained from increasing the dose density of chemotherapy for ER-negative versus ER-positive disease, although some ER-positive patients do benefit from more aggressive chemotherapy. A high research priority is to identify those ER-positive patients who will benefit from multi-agent chemotherapy. Subset analyses have also shown that patients with progesterone receptor (PR)-negative disease may benefit from taxane-based chemotherapy, regardless of ER status. Furthermore, adjuvant trastuzumab should be considered in human epidermal growth factor receptor-2-positive patients who have a moderate/high risk of recurrence. These molecular classifications are being used to design clinical trials to enable adjuvant treatment recommendations to be made based not only on prognostic factors but also on predictive factors for benefit. In future, therapies will increasingly target particular molecular subsets and, as a result, become more effective.

1. Introduction

Breast cancer is a heterogeneous disease that can be classified by variations in gene expression patterns [1]. Traditionally, adjuvant therapy recommendations for early-stage breast cancer (ESBC) have been made based on prognostic factors including: lymph node status, tumour size and hormone receptor status. An evolving approach to assessment of treatment needs is based on the analysis of biological characteristics such as oestrogen receptor (ER) and progesterone receptor (PR) status, human epidermal growth factor receptor (HER)2 status, and by profiling expression patterns of mRNAs that identify biological subclasses of breast cancer. The molecular classification of tumours can facilitate adjuvant treatment recommendations, based not only on prognostic factors such as anatomical staging but also on predictive factors for benefit. Furthermore, a single prediction score for outcome in node-negative, ER-positive ESBC can be obtained with reverse-transcription–polymerase chain reaction to reliably measure the level of ER mRNA (correlating closely

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with the ER protein level), and the expression of ER-regulated genes, HER2, proliferation-related and invasion genes [2]. Therefore, clinical trials have been designed to evaluate adjuvant chemotherapy and hormonal therapy breast cancer subsets in order that the most effective treatment can be found for specific groups.

2. Treatment is dependent on receptor expression

The ninth St Gallen (Switzerland) expert consensus panel suggested that patients with hormone non-responsive disease be offered chemotherapy, while those with hormone-responsive disease should be offered endocrine therapy as the adjuvant therapy, adding chemotherapy for some intermediate-risk and all high-risk groups [3]. Both chemotherapy and endocrine therapy should be given to all patients whose disease has an uncertain level of hormone responsiveness, except if they are at low risk. Breast cancers exhibit a range of hormone receptor levels, and, accordingly, will obtain varying degrees of benefit from adjuvant chemotherapy. This conceptual framework has formed the basis for the Microarray in Node Negative Disease May Avoid Chemo-Therapy (MINDACT) study and the Trial Assessing Individualized Options for Treatment (TAILORx) in Europe and the USA [4].

2.1. *Adding chemotherapy to tamoxifen: the effect of ER status*

Data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B20 study provided justification for the approach recommended at the St Gallen meeting. Both pre- and post-menopausal patients with lymph-node-negative, ER-positive disease were randomised to receive tamoxifen alone, tamoxifen added to cyclophosphamide plus methotrexate plus 5-fluorouracil (CMF) or tamoxifen added to methotrexate plus 5-fluorouracil (MF) chemotherapy [5]. The trial demonstrated a recurrence-free survival (RFS) advantage in patients who had received chemotherapy plus tamoxifen (89% vs. 79%; $P < 0.0001$) and a better, although non-significant overall survival (OS) (87% vs. 83%; $P = 0.063$) after 12 years' follow-up [5]. Patients who had high ER levels ($\geqslant$50 fmol/mg) gained some benefit (absolute benefit 6%) from the addition of CMF or MF to tamoxifen [hazard ratio, HR = 0.67 (95% confidence interval (CI) 0.46–0.97)] at the median 12-year follow-up, but those with lower ER levels (10–49 fmol/mg) showed greater improvement in RFS on chemotherapy, with an absolute benefit of 14% [HR = 0.38 (95% CI 0.25–0.57)] [5]. These data suggest that the degree of benefit gained by a patient from adjuvant CMF/MF is inversely proportional to their level of ER expression.

Prior to this, the International Breast Cancer Study Group published a sub-population treatment effect pattern plot (STEPP) analysis in post-menopausal, node-negative, ER-positive patients randomised to treatment with tamoxifen alone or to tamoxifen combined with CMF [7]. Mature results from this trial showed no benefit with the addition of CMF to tamoxifen. However, on evaluating the population by quantitative ER expression in relation to the 5-year disease-free survival rate (DFS), benefit from the addition of CMF was observed to accrue in patients with very low levels of ER (Figure 1). There was no benefit seen with addition of CMF to tamoxifen in patients with intermediate or high ER levels.

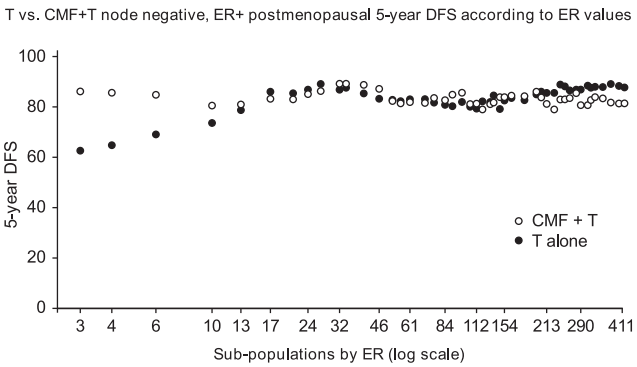

Fig. 1 – Comparison of DFS between patients receiving CMF plus tamoxifen versus tamoxifen alone. DFS: disease-free survival rate; CMF: cyclophosphamide, methotrexate and 5-fluorouracil; T: tamoxifen; ER: oestrogen receptor. Reproduced with permission from Oxford University Press [6].

2.2. *Outcome of sequential chemotherapy then tamoxifen versus concomitant therapy*

The Intergroup 0100 trial (SWOG-8814) demonstrated that in post-menopausal, node-positive, ER-positive patients, cyclophosphamide plus doxorubicin plus 5-fluorouracil (CAF) followed by tamoxifen was associated with a DFS and OS advantage compared with tamoxifen alone [8]. This led to the widespread adoption of anthracycline-based chemotherapy for post-menopausal, node-positive, ER-positive patients. However, a subset analysis in patients with strong ER expression did not show any benefit from adding CAF to tamoxifen, although there was a trend towards benefit with CAF followed by tamoxifen when compared with a concomitant schedule of CAF plus tamoxifen in the strongly ER-positive subset [8].

2.3. *Effects of increased dose density depend on ER status*

A recent analysis of patients with node-positive breast cancer from the Cancer and Leukemia Group B and US Breast Cancer Intergroup compared the incremental benefit of low-dose chemotherapy (CAF) with dose-dense doxorubicin plus cyclophosphamide (AC) followed by paclitaxel [9]. For node-positive, ER-negative disease, data showed that moving from low-dose CAF to dose-dense

chemotherapy resulted in a large absolute benefit in 5-year DFS and OS of 23% and 17%, respectively. In the ER-positive population, however, the benefit was much less than observed in the ER-negative population. ER-positive patients gained a 7% absolute benefit in DFS with dose-dense chemotherapy compared with low-dose CAF, and a 4% improvement in OS. Some ER-positive patients benefit from more aggressive chemotherapy, and as such, there is a high clinical research priority to identify which of the ER-positive patients benefit most.

2.4. HER2 and TOPOIIα status

HER2 status appears to predict whether a patient will benefit from adjuvant anthracycline-containing chemotherapy. In the Mammary.5 (MA.5) study, Pritchard et al. reported that pre-menopausal patients with node-positive *HER2*-amplified breast cancer benefited substantially more from the anthracycline-containing regimen cyclophosphamide plus epirubicin plus fluorouracil (CEF) versus CMF with respect to RFS (HR = 0.52; 95% CI 0.34–0.80; P = 0.003) and OS (HR = 0.65; 95% CI 0.42–1.02; P = 0.06). In contrast, in patients whose tumours lacked amplification of *HER2* there was no difference in 10-year RFS (HR = 0.91; 95% CI 0.71–1.18; P = 0.49) or OS (HR = 1.06; 95% CI 0.83–1.44; P = 0.68) with CEF versus CMF treatment [10].

However, it has been suggested that amplification of the target enzyme of the anthracyclines, topoisomerase II alpha (TOPOIIα), rather than *HER2* status, may predict response to anthracyclines. The MA.5 trial randomised 710 pre-menopausal node-positive patients to receive adjuvant CEF or CMF, and recent data presented at The American Society of Clinical Oncology (ASCO) 2006 meeting showed that amplification or partial deletion of *TOPOIIα* predicted a greater OS benefit from CEF than CMF. Conversely, patients with a normal *TOPOIIα* gene copy number (whose breast cancers were generally HER2-negative) benefited equally from CEF and CMF over 10 years of follow-up [11]. Similarly, the Danish DBCG89D study, which evaluated TOPOIIα as a predictive marker for benefit from adjuvant treatment with CEF versus CMF in high-risk breast cancer patients, showed that *TOPOIIα* amplification or deletion predicted for greater benefit from CEF compared with CMF, while patients with normal *TOPOIIα* status benefited equally from CEF and CMF [12].

3. Treatment with anthracycline regimens: Cardiotoxic concerns

There is limited knowledge on long-term cardiac sequelae related to the use of anthracyclines in the adjuvant setting [13,14]. Two analyses presented at the ASCO 2006 meeting described long-term cardiotoxicity rates associated with anthracycline treatment. The first was an observational study from the Surveillance, Epidemiology, and End Results/Medicare data registry. The study reported that the respective 5- and 10-year rates of congestive heart failure (CHF) in women aged 66–70 years were 19% and 47% for the anthracycline-pre-treated cohort, 14% and 33% for the non-anthracycline chemotherapy pre-treated cohort, and 12% and 28% for the cohort of women not treated with chemotherapy (multivariate Cox regression analysis). The adjusted HR for having a history of CHF was 1.45 (95% CI 1.19–1.76) for anthracycline chemotherapy versus other chemotherapy and 0.97 (95% CI 0.82–1.14) for no chemotherapy versus other chemotherapy. Although the anthracycline-treated patients tended to be younger and have lower co-morbidity scores than those treated with other types of chemotherapy, the rates of CHF among anthracycline-treated women were significantly higher [15].

The second analysis, taken from the National Cancer Institute of Canada Clinical Trials Group MA.5 trial, compared CEF with CMF as adjuvant chemotherapy for breast cancer in younger (median age 45 years) patients. At a median follow-up of 60 months, decreases in left ventricular ejection fraction (LVEF) of >10% were seen in up to 25% of women who received CEF at a cumulative epirubicin dose of 720 mg/m^2, and in up to 10% of patients who received CMF [16].

An earlier study, by Zambetti et al., involved 1000 patients from three prospective trials. Patients were divided into those treated with chemotherapy containing doxorubicin and those who had been given CMF. All but two patients who underwent breast-conserving surgery received breast irradiation. The results showed cumulative cardiac-related mortality in 0.6% of doxorubicin-treated patients versus 0% in CMF-treated patients. Eighteen (5%) of the 355 patients undergoing cardiac evaluation after a median follow-up of 11 years had systolic dysfunction, which was higher in doxorubicin-treated (15 of 192; 8%) than in CMF-treated patients (three of 150; 2%) [13].

Another study, by Bonneterre et al., evaluated the effect of dose escalation of epirubicin (50 or 100 mg/m^2) when combined with fluorouracil plus cyclophosphamide (FEC). After a median follow-up of 102 months, five FEC100-treated patients had an LVEF of <50% and two had developed CHF. Furthermore, asymptomatic left ventricular dysfunction (LVD) was assessed by a peer-review panel blinded to adjuvant chemotherapy randomisation. LVD developed in 18 patients following treatment with FEC100 and in one patient in the group after receiving FEC50. The relationship between cardiac impairment and adjuvant chemotherapy was classified as unrelated, doubtful, possible, or probable according to concomitant risk factors. Among these 18 patients, the LVD was mild (grade 1) in nine patients (doubtful causality, n = 3; possible causality, n = 3; probable causality, n = 3), and moderate (grade 2) in nine patients (possible

causality, n = 4; probable causality, n = 5) [17]. These results demonstrate the potential for persistent deleterious cardiotoxic effects with anthracycline treatment.

4. Impact of progesterone receptor status on therapy

Data from two recent adjuvant trials involving taxane chemotherapy suggest that PR status may predict for taxane benefit. In the US Oncology 9735 study, by Jones et al., 1016 pre- and post-menopausal patients (50% of whom were lymph-node-negative and 70% hormone-receptor positive) were randomised to receive four cycles of standard doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) versus four cycles of docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2 (TC), every 3 weeks [18]. At 5 years' median follow-up, there was a significant absolute DFS advantage of 6% (HR = 0.67; P = 0.016), and a non-significant absolute improvement in OS of 3% (P = 0.13), in favour of the TC combination [18]. TC was better tolerated, with less cardiac toxicity and less nausea and vomiting compared with AC, but there was a slight increase in the incidence of arthralgias, myalgias and febrile neutropenia with TC. In an exploratory subset analysis, TC was superior to AC in patients irrespective of menopausal, ER or node status.

A hypothesis-generating subset analysis was conducted to ascertain whether PR-negative status conferred a greater benefit from TC than PR-positive status in patients with ER-positive disease. The hormone receptor status was assessed by local pathology laboratories. Analysis showed that 85% of the ER-positive patients were both ER-positive and PR-positive. At 4 years of follow-up, the DFS was 89% vs. 84% for TC vs. AC in the PR-positive group compared with 84% and 68% in the PR-negative subset of patients with ER-positive disease [*Unpublished observation; O'Shaughnessy J*]. This larger benefit with TC over AC in ER-positive/PR-negative patients suggests that PR-negative disease may particularly benefit from taxane-based chemotherapy.

The second study, a phase III trial (ECOG-2197) of doxorubicin plus docetaxel (AT) versus AC for node-positive and high-risk node-negative breast cancer, showed no difference in DFS or OS between the two treatment regimens at 59 months' median follow-up [19]. Exploratory subset analyses showed that the ER-negative/PR-negative population benefited to a greater extent from AT than from AC (85 events [n = 454] vs. 109 events [n = 463]; HR = 1.30 [95% CI 0.96–1.70]), as did the ER-positive/PR-negative population (22 events [n = 162] vs. 34 events [n = 164]; HR = 1.64 [95% CI 0.96–2.80]), while the ER-positive/PR-positive subgroup benefited more from AC (73 events [n = 770] vs. 91 events [n = 767]; HR = 0.79 [95% CI 0.58–1.10]) (Figure 2) [19]. These data from ECOG-2197 and the US Oncology 9735 study [18] suggest that the taxanes may be of benefit to ESBC patients with PR-negative disease, regardless of ER status.

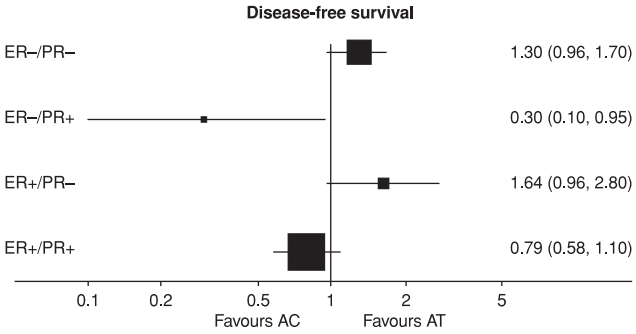

Fig. 2 – DFS in ER/PR subgroups treated with doxorubicin plus docetaxel or doxorubicin plus cyclophosphamide. ER: oestrogen receptor; PR: progesterone receptor; AC: doxorubicin plus cyclophosphamide; AT: doxorubicin plus docetaxel. From the ECOG 2197 protocol presented at ASCO 2005. Used with permission from Dr L. Goldstein [19].

Taxanes have made a significant impact on breast cancer treatment, particularly in PR-negative and HER2-positive patients. TC appears to be more efficacious than AC in all analysed subsets [18], while AT has no treatment advantage over AC except in PR-negative patients [19]. TC avoids the cardiac toxicity of AC and should be adopted as a new standard therapy in patients with intermediate risk, HER2-negative breast cancer.

5. Novel antimetabolites for early-stage breast cancer

5.1. Gemcitabine

Considerable experience has been gained both with single-agent and combination chemotherapy with gemcitabine in metastatic breast cancer (MBC). DFS and OS advantages for gemcitabine plus paclitaxel compared with paclitaxel alone have been observed in first-line MBC patients previously treated with doxorubicin [20]. The superior efficacy of the gemcitabine plus paclitaxel combination suggested that there was sufficient non-cross-resistance of gemcitabine in MBC to justify adjuvant and neo-adjuvant studies designed definitively to assess whether gemcitabine will improve the outcome in ESBC patients.

Trials

The tAnGo trial is a randomised phase III trial examining adjuvant treatment with epirubicin plus cyclophosphamide for four cycles followed by either paclitaxel alone or paclitaxel combined with gemcitabine for four cycles in ESBC patients. The study closed in

2004 with 3152 patients enrolled and interim results are expected soon [21].

The NSABP B38 trial plans to enroll 3400 patients randomised to standard docetaxel 75 mg/m^2 plus doxorubicin 50 mg/m^2 plus cyclophosphamide 500 mg/m^2 (TAC) for six cycles, versus dose-dense doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 followed by dose-dense paclitaxel 175 mg/m^2 (AC-P), versus dose-dense doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 followed by dose-dense paclitaxel 175 mg/m^2 plus gemcitabine 2000 mg/m^2 (AC-PG). Accrual to this study is rapid and ongoing, and is expected to be completed soon.

5.2. *Capecitabine*

Capecitabine is also substantially non-cross-resistant with anthracyclines and taxanes in the metastatic setting, and improves survival when combined with docetaxel compared with docetaxel alone. This justified its assessment in the US Oncology 01-062 adjuvant trial where a final total of 2600 patients were randomised to AC followed by docetaxel alone (100 mg/m^2) versus AC followed by docetaxel plus capecitabine (75 mg/m^2 and 825 mg/m^2) dosed orally twice daily for 14 days on then 7 days off. An interim analysis of this trial will occur in 2007. Capecitabine provides substantial clinical benefit in MBC and it is likely that this agent will further improve the outcome of ESBC patients who benefit from chemotherapy.

NSABP B40 is a neoadjuvant ESBC study comparing docetaxel, docetaxel plus capecitabine, and docetaxel plus gemcitabine, all followed by four cycles of AC. These three groups are also randomised to receive bevacizumab or not during chemotherapy. Those patients who are given bevacizumab continue to receive it until surgery.

These trials will evaluate the role of antimetabolites in biological subsets of ESBC patients.

6. HER2-positive disease and trastuzumab

In the Breast Cancer International Research Group-006 (BCIRG-006) trial, HER2-positive patients (n = 3222) with lymph-node-positive or high-risk lymph-node-negative disease were randomised to either a control arm of AC followed by docetaxel (AC-T), or to one of two investigational arms: (1) AC-T plus trastuzumab (AC-TH), or (2) docetaxel and carboplatin plus trastuzumab (TCH), at a median follow-up of 36 months [22]. Trastuzumab was given concomitantly in the TCH arm and concomitantly with docetaxel in the AC-TH arm. Both trastuzumab-containing regimens were statistically superior to AC-T alone with regard to DFS. The HR for DFS in the AC-TH arm compared with AC-T was 0.61 ($P < 0.0001$), while for TCH compared with AC-T, the HR was 0.67 ($P = 0.0003$). AC-TH was slightly numerically superior to TCH in reducing the rate of breast cancer recurrence, but there was no statistical difference in recurrence between the two trastuzumab treatment arms.

A preliminary analysis of a subset of the patients in the BCIRG-006 trial showed that 35% of patients' cancers had an amplified *TOPOIIα* gene, the target enzyme for doxorubicin. This subset of patients benefited approximately equally from AC-T, AC-TH and TCH regarding DFS on an exploratory analysis. Conversely, in the two-thirds of patients with a *TOPOIIα* copy number that was not amplified, AC-TH and TCH were approximately equally effective and were significantly superior to AC-T in terms of DFS. There was less cardiac toxicity with TCH, and therefore, this regimen can be considered as an appropriate adjuvant treatment for HER2-positive patients, especially those at elevated risk for cardiac toxicity from AC-TH [22].

The Finnish Herceptin (FinHER) study randomised 1010 women with axillary-node-positive or high-risk node-negative (stage II–III) cancer to receive three cycles of docetaxel followed by three cycles of 5-fluorouracil, epirubicin (60 mg/m^2) and cyclophosphamide (FEC60) or to three cycles of vinorelbine followed by three cycles of FEC60 [23,24]. The 232 women with *HER2*-amplified cancers were further randomised to receive weekly trastuzumab for 9 weeks concurrent with either the docetaxel or vinorelbine arms. In the overall treated population, the RFS at 3 years was superior with docetaxel versus vinorelbine [91% vs. 86%; HR for recurrence or death = 0.58 (95% CI 0.40–0.85; $P = 0.005$)], but OS did not differ between groups ($P = 0.15$). Within the subgroup of *HER2*-amplified patients, those who received trastuzumab had a significantly greater 3-year RFS than those who did not [89% vs. 78%; HR for recurrence or death = 0.42 (95% CI 0.21–0.83; $P = 0.01$)] [24]. In this study, trastuzumab was not associated with any significant cardiac toxicity.

The clinical implications of these data are that adjuvant trastuzumab should be strongly considered in patients with HER2-positive disease with a moderate or high risk of recurrence. The optimal approach, whether trastuzumab is used concurrently or sequentially with chemotherapy as was the case in the HERceptin Adjuvant (HERA) trial [25], has yet to be conclusively established. The present standard of care is 1 year of trastuzumab, although a randomised trial evaluating the duration of trastuzumab is justified. There still remains a role for anthracyclines in HER2-positive breast cancer, but it is reasonable to consider the TCH regimen for HER2-positive patients in order to substantially decrease the risk of cardiac toxicity.

The next goal in the treatment of HER2-positive breast cancer is to design adjuvant trials aimed at reducing the risk of recurrence in the central nervous system. Data from the N9831, B-31 and HERA adjuvant trials

show that the central nervous system is a common site of recurrence in a small minority of patients who have been treated with trastuzumab-based therapy [25,26]. Recent phase III data in trastuzumab-resistant HER2-positive MBC [27] have suggested that combined lapatinib and capecitabine are more effective than capecitabine alone in treating brain metastases. Adjuvant lapatinib trials with and without trastuzumab will begin in the near future.

In essence, retrospective data suggest that adjuvant anthracycline treatment benefits patients with HER2-positive tumours with *TOPOII*α amplification/deletion, while HER2-negative patients with normal *TOPOII*α status have equivalent outcomes with CEF and CMF. Prospective trials to evaluate a standard anthracycline versus a non-anthracycline regimen in HER2-negative patients are warranted. Exploratory subset analyses also suggest a benefit from taxane therapy in HER2-positive and PR-negative ESBC.

7. Hormonal therapy in post-menopausal women

Attention is increasingly being paid to ER-positive patients at risk for late relapse from breast cancer, particularly the ~50% who will relapse between years 6 and 15 following diagnosis. In the Mammary.17 (MA.17) trial, 5187 post-menopausal patients received 5 years of tamoxifen after which they were randomised to receive the aromatase inhibitor letrozole or placebo. There was a significant reduction in the risk of relapse with letrozole after 2.5 years of treatment, and the study was unblinded at the first pre-planned interim analysis [28].

In the MA.17 trial, the benefit of letrozole over placebo was most pronounced in women with ER-positive/PR-positive (60 events [3%] vs. 117 events [6%], respectively; HR = 0.50 [95% CI 0.36–0.68]). In contrast, a lack of benefit with letrozole, following 5 years of tamoxifen, was seen in women with ER-positive/PR-negative disease (19 events [6%] vs. 17 events [5%], respectively; HR = 1.19 [0.62–2.29]). The results show that the effect of letrozole following 5 years of tamoxifen appears more pronounced in women with the most hormone-responsive ER-positive/PR-positive tumours [29].

After unblinding, patients who had previously received placebo were allowed to switch to letrozole therapy. Information was available on 2247 women originally assigned to placebo who were free of recurrence at unblinding. Three-quarters of patients originally in the placebo arm (n = 1655) opted to switch to letrozole, while one-quarter (n = 613) declined letrozole treatment. The patients who opted for letrozole had higher-risk tumour characteristics than those who requested no further treatment [28,29]. At interim analysis, there were 342 breast cancer events and 211 deaths across the three groups (those patients randomised originally to letrozole, or to placebo but crossed over to letrozole, or those who stayed on placebo). The median follow-up was 49 months. Results from the crossover of MA.17 showed that after 2 years' treatment with letrozole (versus no treatment) in patients initially receiving placebo, the risk of breast cancer recurrence was reduced by 69% ($P < 0.0001$); risk of distant breast cancer recurrence was reduced by 72% ($P = 0.002$) and risk of death was reduced by 47% ($P = 0.05$) [28].

Ingle et al. conducted an analysis of the MA.17 trial to examine the relationship between the duration of letrozole therapy and hazard for recurrence in the extended adjuvant setting. The results showed that, for patients receiving placebo, there was an increasing risk of disease recurrence over time after discontinuing tamoxifen. For letrozole patients, the risk of recurrence appeared to peak at around 2 years of treatment and decrease thereafter. The HR (letrozole/placebo) for recurrence showed a statistically significant ($P = 0.02$) trend to a decrease over time, indicating a greater benefit of letrozole over time. Thus, analysis of the HRs for disease recurrence over time indicated that for at least out to 4 years, the longer patients are exposed to letrozole, the greater the benefit [30].

Important questions remain unanswered regarding the optimal hormone therapy for post-menopausal patients. Is long-term use of an aromatase inhibitor beyond 5 years needed for patients with high-risk ER-positive and PR-positive disease? Do some patients benefit more from tamoxifen therapy for 2–5 years followed by an aromatase inhibitor, or from prolonged tamoxifen treatment alone? Do patients with ER-positive/PR-negative breast cancer benefit from tamoxifen? In NSABP B-14, ER-positive patients with a high recurrence score did not benefit from tamoxifen [2], and a recent analysis of a large adjuvant population showed less benefit from adjuvant tamoxifen in patients with ER-positive/PR-negative disease compared with ER-positive/PR-positive disease [31]. Virulent, high-grade ER-positive patients, whose risk of recurrence is highest in the first 5 years, appear to benefit most from 5 years' treatment with an aromatase inhibitor, while there seems to be a strong rationale for recommending extended adjuvant therapy for indolent ER-positive and PR-positive ESBC, and switching from tamoxifen to an aromatase inhibitor provides a proven option to achieve longer term therapy in such patients.

8. Conclusion

In summary, interpreting systemic adjuvant therapy data with the aid of molecular classification leads to hypotheses that can be tested in definitive prospective trials in defined breast cancer subtypes. Molecular classification will increasingly enable adjuvant treatment

recommendations to be made based on predictive factors for benefit rather than based on traditional prognostic factors such as anatomical staging. In the next decade, adjuvant therapy will become increasingly specific towards particular molecular subsets and, as a result, far more effective.

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