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The role of adjuvant systemic therapy in patients with operable breast cancer

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Introduction

The mortality from breast cancer has fallen by over 15% in the UK over the last 15 years, despite a rising incidence.[1] Historically over half of women with operable breast cancer who received loco-regional treatment alone died from metastatic disease, indicating the presence of micrometastases. Traditionally, the major risk factors for recurrence have been the involvement of axillary nodes, poor histological grade, large tumour size and histological evidence of lymphovascular invasion around the tumour site. The absence of oestrogen and progestogen receptor (ER and PR) and the overexpression of human epidermal growth factor receptor 2 (HER2) also carry an adverse prognosis. Over recent years it has been increasingly recognised that breast cancer comprises a number of biological subtypes, each with a distinct behaviour and prognosis, and increasingly molecular factors rather than these classical histopathological features are being used to determine the degree of residual risk after breast cancer surgery, and so aid judicious use of potentially toxic treatments.[2] Gene expression profiling has emerged as a new determinant of recurrence risk and a major current challenge is to integrate this technology into treatment planning.

Following surgery, and the identification of the risk profile of an individual patient, adjuvant systemic medical therapy with endocrine therapy, chemotherapy and targeted biological therapies, alongside radiotherapy, may improve survival and delay or prevent relapse in early breast cancer.

Adjuvant endocrine therapy

Since the observation by Beatson more than 100 years ago that oophorectomy could induce regression of advanced breast cancer,[3] endocrine therapy has proved to be one of the most valuable therapies in cancer medicine. Approximately 75% of invasive breast cancer patients present with hormone receptor-positive disease,[4] where the oestrogen receptor (ER) pathway is key for the growth of these cancers. Modulation of ER activation, therefore, is an essential component of treatment in ER-positive disease.

Endocrine therapy in premenopausal women

Tamoxifen

Until recently 5 years of tamoxifen was the standard adjuvant endocrine therapy for both pre- and postmenopausal women. The results of an overview of tamoxifen trials involving around 21 000 women carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have shown that tamoxifen given for 5 years reduces the risk of death by around one-third (relative risk (RR) = 0.71 ± 0.07).[5] The proportional reduction is not significantly affected by age, nodal status or use of chemotherapy; the absolute benefit naturally relates to the absolute risk. The reduction in the risk of recurrence is seen both during the 5 years of treatment (RR = 0.53 ± 0.03) and extends into years 5–9 (RR = 0.70 ± 0.06). The benefits were similar and highly significant in both ER-positive/progesterone receptor (PR)-positive

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and ER-positive/PR-negative disease. The reduction was greater in strongly positive ER disease (RR = 0.51 ± 0.07) than in weakly ER-positive disease (RR = 0.65 ± 0.07)[5].

These benefits have to be viewed in the light of side-effects, including vasomotor symptoms, and a small but significantly increased risk of developing uterine carcinoma and thromboembolism. Combined, these two conditions are associated with a 10-year mortality of 0.2%.[5]

The duration of adjuvant tamoxifen has been under ongoing investigation for decades. A meta-analysis studying 1-, 2- and 5-year durations of adjuvant tamoxifen was reported by the EBCTCG. In the 55 clinical trials reviewed (consisting of approximately 30 000 women), with 1, 2, and 5 years of adjuvant tamoxifen, the reductions of recurrence observed during 10 years of follow-up were 21% (standard deviation [SD] 3), 29% (SD 2) and 47% (SD 3), respectively (P <0.00001). The corresponding proportional breast cancer mortality reductions were 12% (SD 3), 17% (SD 3) and 26% (SD 4), respectively (P = 0.003; EBCTCG, 1998[6]).

The pivotal randomised, placebo-controlled clinical trial NSABP B-14 (National Surgical Adjuvant Breast and Bowel Project B-14),[7] investigated 5 years of tamoxifen versus placebo in operable, ER-positive, lymph node-negative breast cancer patients. Results were consistent with the data from EBCTCG; there is a benefit in disease-free survival (DFS) with 5 years of treatment. Long-term follow-up at 10 years revealed that DFS was superior in the tamoxifen arm versus the placebo arm: 69% vs 57% (P < 0.0001).[7] Distant DFS was 76% vs 67%, respectively (P <0.0001). Overall survival was also in favour of the treatment arm: 80% vs 76% (P = 0.02). As a result of the data accumulated in these trials, for many years 5 years has been the standard duration of tamoxifen treatment.

However, in 2013 the results of two trials looking at duration of tamoxifen of longer than 5 years were published. The Adjuvant Tamoxifen: Longer against Shorter (ATLAS)[8] trial included 12 894 women who had completed 5 years of adjuvant tamoxifen. Patients were randomised to either continue tamoxifen for an additional 5 years, or to stop endocrine treatment. Women completing 10 years of treatment had a significant reduction in risk of breast cancer recurrence, reduced breast cancer mortality and overall mortality. Importantly, a reduction in both recurrence and mortality rate were evident following 10 years of treatment, rather than during years 5–9 (recurrence rate ratio [RR] 0.90 [95% CI 0.79–1.02] during years 5–9 and 0.75 [0.62–0.90] in later years; breast cancer mortality RR 0.97 [0.79–1.18] during years 5–9 and 0.71 [0.58–0.88] in later years). This demonstrates a benefit with an additional 5 years of treatment as well as a possible carryover effect from the tamoxifen.

A similarly designed UK study, Adjuvant Tamoxifen: To offer More? (ATTOM)[9] included 6953 women with ER-positive or unknown ER status breast cancer who were disease free after 5 years of tamoxifen. They were randomised to complete a total of 10 years of tamoxifen, or to stop after 5 years. As with the ATLAS study, a similar benefit was demonstrated with 10 years of tamoxifen. There was a reduced rate of breast cancer recurrence (P = 0.003) in a time-dependent manner; RR was 0.99 during years 5–6, 0.84 in years 7–9 and 0.75 later. Breast cancer mortality was also reduced (P = 0.05). The common toxicities associated with tamoxifen were hot flushes, vaginal discharge, an increased risk of venous thromboembolism and endometrial cancer, but the absolute risk for the latter was less than 1%.

As a result, 10 years of tamoxifen is now routinely considered in all but the lowest risk premenopausal women taking adjuvant tamoxifen. However, in a subgroup of premenopausal women who are at high risk there may be a rationale to add ovarian function suppression as a component of the adjuvant endocrine therapy strategy.

✔✔ Five years of tamoxifen is recommended for premenopausal women with oestrogen receptor-positive breast cancer. It may also be considered for lower-risk postmenopausal women. Extension of treatment to 10 years may be considered, although absolute benefit is small.

Tamoxifen has been the mainstay of adjuvant endocrine therapy for premenopausal women for many years. Similar benefits are seen in premenopausal women as in postmenopausal women (Table 15.1).[4] However, there has also been a longstanding debate as to the potential benefit of ovarian function suppression (OFS). OFS can be achieved by LHRH (luteinising hormone-releasing hormone) agonists (such as goserelin), bilateral oophorectomy or bilateral ovarian irradiation.

Table 15.1 • Outcomes for oestrogen receptor-positive patients with ~5 years tamoxifen, by age at trial entry

Age	<45 years	45–54 years	55–69 years
Risk reduction for recurrence	0.63	0.72	0.54
Risk reduction for breast cancer mortality	0.71	0.82	0.63

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In the INT-101 trial, the addition of goserelin and tamoxifen to standard adjuvant therapy with CAF (cyclophosphamide, adriamycin and fluorouracil) significantly improved DFS; 9-year DFS rates were 57% for CAF, 60% for CAF plus goserelin, and 68% for CAF plus goserelin and tamoxifen.[10] An unplanned retrospective analysis of these data suggested that the addition of goserelin to CAF was most beneficial in those women under the age of 40. However, the trial did not examine the addition of goserelin to CAF and tamoxifen, which by the time of completion, was regarded as the standard of care.

In 2003, the International Breast Cancer Study Group (IBCSG) initiated two randomised trials, SOFT and TEXT. Eligible patients were premenopausal women with ER-positive breast cancer who had undergone complete surgical excision of primary breast cancer and radiotherapy when deemed necessary. The SOFT (Suppression of Ovarian Function) prospective Trial randomly assigned 3066 premenopausal women to receive either 5 years of tamoxifen, tamoxifen plus ovarian suppression (OFS) or exemestane and ovarian suppression.[11] Patients were stratified according to prior receipt or non-receipt of chemotherapy. Interestingly, adding ovarian suppression to tamoxifen did not provide significant benefit to the overall study population. However, ovarian suppression improved disease-free survival in those women who were deemed to have sufficient risk to warrant adjuvant chemotherapy, where there was a non-significant disease-free survival benefit of 3.6% with OFS and tamoxifen over tamoxifen alone. The group of women who derived the greatest benefit were those who were under the age of 35 (94% of whom received chemotherapy). The 5-year DFS in this population was 67.7%, 78.9% and 83.4%, for tamoxifen alone, tamoxifen and OFS, and exemestane plus OFS, respectively.

The Tamoxifen and Exemestane Trial (TEXT) was designed to evaluate exemestane plus OFS against tamoxifen and OFS amongst premenopausal women. The combined analysis from SOFT and TEXT of over 4000 patients showed a significant benefit with adjuvant exemestane–OFS compared with tamoxifen–OFS in premenopausal women with hormone receptor-positive breast cancer.[11] There was a significant improvement in DFS; 91.1% in the exemestane–OFS group and 87.3% in the tamoxifen–OFS group at 5 years and a 34% relative risk reduction in disease recurrence. Among patients who received chemotherapy, there was an increased proportion of patients without breast cancer recurrence at 5 years in exemestane–OFS by 5.5.percentage points, compared to tamoxifen–OFS in TEXT and 3.9 percentage points in SOFT. Although no significant difference in overall survival has been demonstrated, conclusions are premature as follow-up has been for 68 months only.

In summary, ovarian suppression in combination with tamoxifen or exemestane should be considered for premenopausal patients with early breast cancer at sufficient risk to warrant adjuvant chemotherapy. However, the side-effects and impact on quality of life of this treatment should not be underestimated. Adverse grade 3 and 4 events were reported in 30.2% of the patients receiving exemestane–OFS and 29.4% of those assigned to tamoxifen–OFS. The most frequently reported events were hot flushes, musculoskeletal symptoms and hypertension. Grade 3 or 4 depression was reported in 4.1% of the patients, with over 50% reporting the symptom at some level. Osteoporosis (T score $< -2.5\%$) was more common in the exemestane–OFS group than in those receiving tamoxifen–OFS, 13.2% and 6.4%, respectively. Thromboembolic events, hot flushes and urinary incontinence were reported more often by patients receiving tamoxifen–OFS. Endometrial cancers occurred in five patients having tamoxifen–OFS compared to two patients receiving exemestane–OFS.

The optimal time to initiate ovarian suppression therapy requires further investigation. In TEXT, adjuvant ovarian suppression was commenced concurrently with chemotherapy, an average of 1.2 months after surgery. Meanwhile, in the SOFT trial, the cohort of patients who received chemotherapy all completed chemotherapy before ovarian suppression was administered. This was on average 8 months after surgery, with 4 months of adjuvant tamoxifen therapy during the intervening period. Furthermore, OFS was continued for 5 years and a valid question is whether a shorter duration of treatment can provide a similar benefit.

✔ Ovarian suppression has a role in premenopausal women with high-risk disease.

Endocrine therapy in postmenopausal women

Aromatase inhibitors: first-line therapy

✔✔ The aromatase inhibitors anastrozole and letrozole have each been shown to improve DFS compared with tamoxifen when given as first-line adjuvant therapy for a planned 5 years in postmenopausal women with hormone receptor-positive early breast cancer[12–15] (**Fig. 15.1**).

Aromatase inhibitors (AI) are the treatment of choice in postmenopausal women as first-line endocrine therapy. The ATAC (Arimidex, Tamoxifen, Alone or in Combination)[12] trial was the first study to directly compare tamoxifen with an AI.

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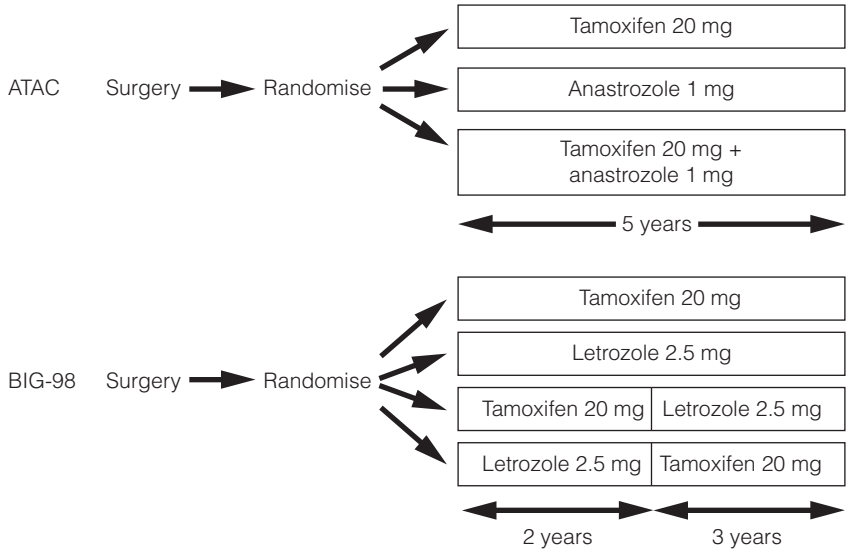

Figure 15.1 • The ATAC and BIG1-98 trial schemes.

A total of 9366 postmenopausal women with early invasive breast cancer were randomised to receive either anastrozole, tamoxifen or a combination of both drugs for a total of 5 years after completion of their surgery and chemotherapy, where required. Patients with ER-negative and unknown ER status were also eligible. However, in women with ER-positive breast cancer, the absolute reduction in recurrence was 2.7% at 5 years and 4.3% at 10 years with Hazard Ratio (HR) 0.86 ($P = 0.003$) for DFS. Interestingly, despite the greatest benefits seen during the first 2 years of active treatment, the differences in DFS remained significant throughout the entire follow-up period and after treatment was completed.

The 100-month analysis of the ATAC trial[13] showed improved disease-free survival (HR 0.85, $P = 0.003$), time to recurrence (HR 0.76, $P = 0.0001$), contralateral breast cancer rate (HR 0.6, $P = 0.004$) and distant recurrence rate (HR 0.84, $P = 0.022$) (Table 15.2). The absolute differences in time to recurrence increased over time; 2.8% at 5 years and 4.8% at 9 years. Recurrence rates were also significantly lower on anastrazole than tamoxifen and remained low after completion (HR 0.75 [0.61–0.94], $P = 0.01$). This demonstrates a larger carryover effect in efficacy seen with anastrazole than has been seen with tamoxifen. However, there were higher fracture rates in patients receiving anastrazole, with an incidence rate ratio of 1.55 ($P < 0.0001$) but the difference was not seen once treatment was completed. There was no overall survival benefit.

The BIG1-98 trial involved 8010 postmenopausal women with ER-positive breast cancer, who were randomised to receive letrozole or tamoxifen alone for 5 years, or a combination of either tamoxifen for 2 years followed by letrozole for 3 years, or letrozole for 2 years followed by tamoxifen for 3 years. With a median follow-up period of 8.7 years, letrozole proved to be significantly better than tamoxifen and there were similar results to the long-term follow-up from ATAC; DFS (HR 0.82, 95% confidence interval (CI) 074–0.92) and overall survival (OS) (HR 0.79, CI 0.69–0.90).[14] The results of these two trials are summarised in Table 15.2.

Comparative toxicities of first-line aromatase inhibitors and tamoxifen

The ATAC and BIG1-98 trials have both shown that tamoxifen is associated with a small but significant increase in the incidence of hot flushes compared with anastrozole or letrozole (4.5–5% increase), vaginal bleeding (3.3–3.7% increase), vaginal discharge (8.6% increase), endometrial carcinoma

Table 15.2 • Results from the ATAC and BIG1-98 trials: comparison of anastrozole (ATAC) and letrozole (BIG1-98) with tamoxifen

	ATAC*	BIG1-98*
No. of patients	6241	8010
Median follow-up (years)	10	8.7
DFS (hazard ratio)	0.85	0.82
5-year DFS difference (%)†	2.8	3.1
OS (hazard ratio)	1.00‡	0.79

*Monotherapy groups only.
†Absolute difference.
‡Non-significant.

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(0.2–0.4% increase) and venous thromboembolism (1.4–2% increase). The ATAC trial has likewise shown a small but significant increase in ischaemic cerebral vascular disease (1.1% increase) with tamoxifen compared with anastrozole, but this has not been confirmed in the BIG1-98 trial compared to letrozole. In contrast, anastrozole and letrozole have been shown to be associated with a statistically significant increase in the incidence of musculoskeletal problems (6.5–8% increase) and fractures (1.7–2.2% increase).

Of note, tamoxifen is associated with a significant increase in gynaecological surgery compared with either of the aromatase inhibitors. In the ATAC trial 5.1% of women had hysterectomies compared with 1.3% on anastrozole. In the BIG1-98 trial 288 women (9.1%) have required endometrial biopsies compared with 77 (2.3%) with letrozole.[14] Women should therefore be appropriately counselled about these risks prior to embarking on treatment.

✔ Bone loss due to aromatase inhibitors means that all of those receiving these drugs should undergo bone density scanning unless already receiving bisphosphonates.

Sequential therapy with aromatase inhibitors after tamoxifen

Until recently, there was considerable interest in trials assessing the benefit of sequential adjuvant aromatase inhibitors given 2–3 years after tamoxifen. For example, in the Intergroup Exemestane double-blind Study (IES), 4274 patients who had already been on tamoxifen for around 2 years were randomised to continuing on tamoxifen or switching to exemestane to complete 5 years of treatment. Updated results with a median follow-up of 91 months have shown a significant reduction in the risk of relapse and an improvement in OS (HR 0.86, 95% CI 0.75–0.99) with the switch.[16] Three other sequential trials involving anastrozole have shown similar results.[17–19]

These results suggested possible superiority of sequential switching over the benefit achieved with first-line aromatase inhibitor therapy in ATAC and BIG1-98.

Two trials have addressed this issue directly, however, and recently reported results. Two of the arms in BIG1-98 compared tamoxifen for 2 years followed by a switch to letrozole with letrozole alone for 5 years and found no significant benefit of the switch compared with letrozole up front (8-year DFS 85.9% vs 87.5%).[20] However, letrozole monotherapy tended to be better than tamoxifen followed by letrozole, particularly in controlling distant recurrences in patients at higher risk of relapse. Nonetheless, switching to tamoxifen after an initial 2 years of letrozole would seem to be a reasonable option for patients who require letrozole cessation for any reason. Similarly, in the TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial, 9779 patients were randomised to tamoxifen for 2–3 years followed by exemestane to complete 5 years or to exemestane up front for 5 years. No significant difference was found in DFS (85% vs 86%) with a median follow-up of 5.1 years.[21]

✔✔ Current evidence therefore suggests that adjuvant use of aromatase inhibitors up front is as effective as switching after 2–3 years of tamoxifen.

Extended adjuvant therapy with aromatase inhibitors: beyond 5 years

The risk of recurrence of early breast cancer continues for at least 10 years after diagnosis and is greater in patients with hormone receptor-positive cancers.[22] In the EBCTCG overview analysis more than half of breast cancer recurrences occur after 5 years.[5]

A seminal trial, NCIC-CTG MA.17/BIG1-97, assessed efficacy of 5 years of letrozole after 5 years of adjuvant tamoxifen.[23] At a median follow-up of 2.4 years, patients receiving letrozole had a significant 43% reduction in the risk of recurrence ($P = 0.00008$) and a non-significant reduction in all-cause mortality. Consequently, the trial was unblinded and patients on placebo were allowed to crossover to letrozole. ITT analysis at 64 months' follow-up showed a persistent 32% benefit in DFS despite 66% of patients on tamoxifen crossing-over to letrozole. Further analysis has confirmed that patients initially assigned to receive letrozole had significantly better DFS (HR 0.52), distant DFS (HR 0.51) and better OS (HR 0.61), compared to control patients.[24] Of note, amongst patients who were deemed premenopausal when starting tamoxifen and who subsequently became postmenopausal during treatment, the reduction in DFS events was 75% (HR 0.26, $P = 0.03$). These data demonstrate the strategy to switch endocrine therapy should be discussed for all premenopausal patients who become postmenopausal during tamoxifen treatment following appropriate consideration of side-effects.

In two similar but smaller trials, extended adjuvant anastrozole (ABCSG-6a) and extended adjuvant exemestane (NSABP B-33), both after 5 years of tamoxifen, showed that extended therapy with an aromatase inhibitor reduces the risk of recurrence significantly.[25,26]

The optimal duration of adjuvant aromatase inhibitor therapy has not yet been established

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but the recent data from the MA17R clinical[27] trial help to answer this important question. The MA17R phase III trial randomised over 1900 postmenopausal women with hormone receptor-positive disease to receive either an additional 5 years of letrozole therapy or placebo, following 5 years of an AI. This study followed MA17 and so a proportion of women, approximately 68%, had initial treatment with 5 years of tamoxifen and 5 years of letrozole, before randomisation for further AI or placebo. The study population included 20% of women who had no prior tamoxifen, but who had completed 5 years of an aromatase inhibitor. Despite this, there is benefit for extended treatment with an aromatase inhibitor with an improvement in 5-year disease-free survival: HR 0.66 (95% CI, 0.48–0.91), and a reduction in the annual incidence rate of contralateral breast cancer: HR 0.42 (95% CI 0.22–0.81). There was no difference in overall survival after a median follow-up of 6.3 years. Although the incidence of toxicities was similar in both groups, patients receiving letrozole had a significantly lower bone mineral density, compared to patients on placebo, with a greater number of women diagnosed with new onset osteoporosis. Among 133 patients who were taking letrozole and who had a fracture, 56% were taking bisphosphonates and 90% were taking calcium supplements. There was no clinically significant difference in the quality of life scores in either group but the women who elected to participate in the trial are likely to have tolerated the initial 5 years of AI treatment, so are a selected population. Consequently, the decision for prolonged therapy with an aromatase inhibitor will largely depend on a number of factors, including the patient's tolerability, quality of life, changes in bone mineral density and an individual risk assessment of recurrence. Therefore it is possible that for some women, prolonged treatment might be the most appropriate strategy but this has to be balanced against the potential risks of prolonged use of aromatase inhibitors. Other trials are continuing to address this question, including NSABP B-42 (5 vs 10 years letrozole) and the ABCG-16 Secondary Adjuvant Long-term Study with Arimidex (SALSA) comparing a further 2 years versus a further 5 years of adjuvant treatment with anastrozole after an initial 5 years of adjuvant endocrine therapy.

Other aromatase inhibitor issues

Aromatase inhibitors are contraindicated in premenopausal women. Likewise, caution must be observed when used in younger women following chemotherapy-induced amenorrhoea. In an audit carried out at the Royal Marsden Hospital, 12 of 45 younger women (27%), median age 47, treated with an aromatase inhibitor following chemotherapy-induced amenorrhoea developed clinical or biochemical return of ovarian function (including up to the age of 53 years).[28] Aromatase inhibitors should therefore be used with great caution in this group of women and ideally serum oestradiol should be monitored using a high sensitivity assay.

Vaginal dryness, atrophy and dyspareunia are significant issues in women on aromatase inhibitors. In a small study, six of seven women given vaginal oestradiol (Vagifem®) while on an aromatase inhibitor developed a significant rise in serum oestradiol from less than 5 pmol/L to a mean of 72 pmo/L (maximum 219 pmol/L) at 2 weeks.[29]

✔ The majority of vaginal oestrogen preparations should not be used in women on aromatase inhibitors unless serum oestradiol levels can be monitored with a high sensitivity assay. Estring® releases very low levels of oestrogen continuously and appears to have very low levels of absorption when compared to oestrogen creams or pessaries. This may well be a better option, although confirmatory studies have not yet been done. The other option is to switch to tamoxifen, which is likely to be of similar efficacy except for high-risk cancers.

See Table 15.3 for a summary of recommendations for adjuvant endocrine therapy.

Table 15.3 • Summary of recommendations for adjuvant endocrine therapy

Menopausal status*	Recommendation
Premenopausal	Tamoxifen 5 years In women <35 years, consider OFS and exemestane particularly if high risk of disease (adjuvant chemotherapy)
Postmenopausal†	Letrozole 5 years or Anastrozole 5 years
Women who are menopausal after 5 years of tamoxifen	Consider: Anastrozole Letrozole Exemestane in high-risk patients
Women who have completed 5 years of aromatase inhibitor	Currently limited data Consider option of continuing in high-risk patients

*Based on pre-chemotherapy menopausal status.
†Caution in women under the age of 50; return of ovarian function on aromatase inhibitor is possible.

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Adjuvant chemotherapy

✔✔ Adjuvant chemotherapy has a significant role in the treatment of early breast cancer. The 2011 Oxford Overview meta-analysis[30] included outcome data from more than 100 polychemotherapy trials (including the oldest of 25 years), for approximately 100 000 randomised women, and reported that combination chemotherapy reduces the annual risk of recurrence by almost 25% and reduces the risk of death by around 14%. Furthermore, greater reductions in breast cancer and overall mortality were shown in comparisons between trials of more modern and older chemotherapy regimens. Most of the effect of adjuvant chemotherapy on the risk of recurrence is seen within the first 5 years after randomisation. Patient selection is critical to the effective and safe use of adjuvant chemotherapy; for some subgroups, the benefit is very much larger than the average and for others, smaller. Adjuvant chemotherapy was initially used in women with involved axillary lymph nodes for whom recurrence risk was highest. It is now clear that many women with node-negative disease also benefit; conversely it is likely that some with node-positive disease do not. The most recent Oxford meta-analysis suggests that the proportional risk reductions associated with taxane- or anthracycline-based chemotherapy regimens are not influenced by age, nodal status or tumour characeteristics.[30] Currently, a great deal of research is focused on identifying with more precision than in the past which patients are likely to benefit from chemotherapy, and in particular those women with oestrogen receptor-positive cancers who benefit, as in these women adjuvant endocrine therapy also improves outcome. Indeed, a poll of international breast cancer specialists indicated that this was the top priority in breast cancer research.[31]

Identifying which patients will benefit from adjuvant chemotherapy

Age

In general, the absolute gain from chemotherapy is higher for younger than older women. It is likely, however, that this difference relates mainly to the biological characteristics of breast cancer being more favourable to chemotherapy response in younger women, rather than an intrinsic adverse interaction between age and chemotherapy efficacy.[32]

Elderly women with breast cancer have been under-represented in clinical trials to date, but this is changing. The Cancer and Leukaemia Group B (CALGB) 49907 trial demonstrated that standard adjuvant chemotherapy was superior to single-agent oral chemotherapy with capecitabine in women over the age of 65, and suggested that the benefit was more pronounced in women with hormone receptor-negative tumours.[33] However, it is also clear that older women experience significantly greater toxicity with adjuvant cytotoxic treatment,[34–37] and there are a number of trials under way that aim to define those elderly patients for whom chemotherapy is most appropriate.

Preserving ovarian function in premenopausal women

Ovarian failure is a common toxicity associated with chemotherapy and amenorrhea can occur in 50% of women undergoing chemotherapy. This is particularly devastating for women who have not yet started or completed their families and may deter young women with high-risk breast cancer from pursuing optimal adjuvant treatment with chemotherapy. Pivotal data from POEMS, the Prevention frOm Early Menopause Study, evaluated ovarian failure rates in premenopausal women with hormone receptor-negative breast cancer, who had anthracycline-based chemotherapy with or without the addition of a GnRH agonist, goserelin.[38] Although missing data weakened the interpretation of the findings, administration of goserelin with chemotherapy appeared to protect ovarian function and improved the prospects of fertility. The ovarian failure rate was 8% in the goserelin group and 22% in the chemotherapy-alone group (OR 0.30; 95% CI 0.09–0.97; two- sided $P=0.04$). There were also improved rates of disease-free and overall survival in the goserelin group, which is of particular interest as an ER-negative population was studied. However, it is difficult to draw meaningful conclusions of any therapeutic effect of GnRH agonists, as disease risk factors were not stratified in this study. In addition, these data are unable to address the safety of GnRH agonist as an ovarian protection strategy in ER-positive breast cancer.

✔ Premenopausal women with a partner and no children who may wish for children in future and are likely to have chemotherapy for breast cancer should be referred for egg harvest to allow for the possibility of in vitro fertilisation.

Nodal status

Initially, adjuvant chemotherapy tended to be reserved for patients with axillary node involvement on the basis of their higher risk. It is now clear that the proportional reduction in the risk of recurrence is similar for those with node-negative as for node-positive disease.[30] Nevertheless, since the absolute risk is greater with nodal involvement, so is the absolute benefit. Although nodal involvement

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carries a worse prognosis, this does not necessarily imply chemotherapy benefit and we are now in an era when molecular markers are at least as important as nodal status in determining chemotherapy benefit (see below).

ER status

There has been considerable controversy over the years as to whether patients with ER-positive disease gain as much from adjuvant chemotherapy as those whose tumours are ER-negative. The 2011 Oxford Overview data indicate that the proportional benefits are very similar, both in older and younger women.[30]

The Overview also indicates an additional benefit for combination chemotherapy over tamoxifen alone for ER-positive tumours, but again, more so for younger than for older women. Recent evidence, however, suggests that the major chemotherapy benefit in ER-positive breast cancer is in selected subgroups and that for many patients with ER-positive cancers there is little or no benefit for chemotherapy (see below).

Molecular markers

The EBCTCG Overview shows that, overall, the survival of patients with hormone receptor-positive disease is significantly improved by chemotherapy over and above tamoxifen, with an HR of 0.66.[30] The important question, however, is to identify those women for whom the gain is large enough to be of real clinical benefit when balanced against toxicity. This relative benefit broadly applies to all patients but the absolute benefit to the patient depends on their risk such that a high-risk patient with a predicted risk of death of 60% at 10 years will gain an absolute benefit of (0.34×60%) ~20% while a low-risk patient with risk of death of 10% would have an absolute benefit of 3% at which point the risks of treatment can outweigh the benefits. Various guidelines for chemotherapy decision-making have been proposed; one of the best recognised is the St Gallen Consensus. In the most recent update, the 2013 St Gallen panel[39] suggested that subtypes of breast cancer can be defined by gene array profiles, and that each subtype differs in its epidemiological risk factors, natural history and response to systemic and local therapies. Surrogate immunohistochemical markers of gene expression array information allow an approximate and simplified classification system of intrinsic subtypes (see Table 15.4). This latest consensus demonstrates a paradigm shift from the use of traditional clinico-pathological features to determine the risk of recurrence, towards an assessment of the underlying biology of the tumour and the use of multigene signatures to provide prognostic information.

Further insight into this issue comes from an analysis of the SWOG 8814 trial, in which postmenopausal women with node-positive hormone receptor-positive tumours were randomised to tamoxifen alone or tamoxifen with anthracycline-containing chemotherapy (cyclophosphamide, adriamycin and 5-fluorouracil).[40] Overall, there was a significant benefit in favour of those receiving chemotherapy concurrently with tamoxifen, but in a retrospective subset analysis patients with a high ER score (Allred score 7 or 8) showed no benefit from the addition of chemotherapy even in the presence of involved nodes. Likewise, women whose tumours were HER2-negative showed no benefit from the addition of chemotherapy unless they had four or more nodes involved. This analysis should be considered as hypothesis-generating rather than being definitive, but emphasises the need to identify molecular markers to predict which patients really benefit from chemotherapy.

Table 15.4 • Intrinsic subtypes of breast cancer and approximation by immunohistochemistry (St Gallen 2011)

Intrinsic subtype	Clinico-pathological definition
Luminal A	'Luminal A-like' ER positive HER-2 negative Ki67 'low' (<14%)* Recurrence risk 'low' based on multi-gene-expression assay (if available)
Luminal B	'Luminal B-like (HER2-negative)' ER-positive HER2-negative and at least one of: Ki67 'high' PgR 'negative or low' Recurrence risk 'high' based on multi-gene-expression assay (if available) Luminal B-like (HER2-positive) ER-positive HER2 overexpressed or amplified Any Ki67 Any PgR
HER2 overexpression	'HER2-positive (non-luminal)' HER2 overexpressed ER absent
Basal-like	'Triple negative (ductal)' ER, PgR absent HER2-negative

* Definition of Ki67 'low' established by comparison with PAM50 intrinsic subtyping.[104]

Gene expression assays

Gene expression analysis has classified breast cancers according to gene expression signatures, to quantify more accurately the likelihood of breast

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cancer recurrence and predict the magnitude of chemotherapy benefit. Recent ASCO guidelines[41] have identified a number of such assays, which have clinical validity and utility. Currently, the most widely used of these is a 21-gene assay now offered as a commercial reference laboratory test (Oncotype DX, Genomic Health Inc.). This is based on formalin-fixed material from which the level of gene expression is used to determine a recurrence score predicting the likelihood of distant recurrence.[42]

The Oncotype DX assay has been applied to a subset of patients in the NSABP B-20 trial, randomising women with node-negative disease to tamoxifen and chemotherapy (CMF or MF) versus tamoxifen alone. It was found that women with a low recurrence score had no significant benefit from chemotherapy, whereas those with a high recurrence score had a major and significant benefit with an absolute decrease in the 10-year rate of distant recurrence of 28% (88% vs 60% free of distant recurrence).[43] Patients with an intermediate recurrence score had a relatively small benefit and such patients are now being included in a trial randomising women with cancers with intermediate scores to chemotherapy or not in addition to endocrine therapy (TAILORx). Oncotype DX has also been validated in ER-positive patients in the ATAC trial[44] and in node-positive patients in SWOG 8814;[45] the key message from these data is that some patients with limited nodal involvement (i.e. 1–3 lymph nodes positive), may not benefit from chemotherapy. However, patients with a low recurrence score but with node-positive disease have a worse prognosis than those with a low recurrence score and node-negative disease. Therefore, the current recommendation from ASCO is for the use of Oncotype DX in ER/PR-positive, HER2-negative and node-negative disease but not in women with node-positive disease.

The question with regard to Oncotype DX is its additional benefit over standard immunohistochemistry. This was addressed in a study where proliferation, as measured by Ki67, was combined with ER, PR and HER2 to form the IHC4 score.[46] The score appeared to further risk-stratify those patients deemed intermediate risk by the Adjuvant Online and Nottingham Prognostic Index (NPI) and correlated closely with Oncotype DX. The main issue with the IHC4 is quality control; there is a lack of reproducibility in measuring Ki67, which continues to be a problem in many laboratories.[47] Similarly, a 70-gene signature (Mammaprint) has also shown strong correlation with outcome[48,49] and identifies a good and a poor prognosis group. A second trial, MINDACT (Microarray In Node- Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy),[50] was a prospective trial looking at the clinical utility of this 70-gene signature assay. In women with early breast cancer, assessment of their genomic risk was determined using the 70-gene signature and their clinical risk by using a modified version of Adjuvant Online. Patients were stratified to receive chemotherapy depending on their risk: those patients who had a high clinical and genomic risk received chemotherapy, while women deemed to have a low clinical and genomic risk did not. Where there was discordance in risk results, either score was used to determine treatment with chemotherapy.

The results revealed that among women with early-stage breast cancer, who did not have chemotherapy despite a high clinical risk but who had a low genomic risk for recurrence, there was a 5-year rate of survival without distant metastasis of 94.7% (95% CI, 92.5 to 96.2), a 1.5 percentage points lower rate than in women who had chemotherapy. These women accounted for a fifth of the study population, and given these findings, approximately 46% of women with high clinical risk may not require chemotherapy. However, further work is required to determine the validity of the various gene assay signature tests in particular clinical scenarios, as there are now a number of tests available.

Chemotherapy schedules

Anthracycline-based chemotherapy

Anthracyclines have been used widely for the last decade or more, and have largely replaced older CMF (cyclophosphamide/methotrexate/fluorouracil) regimens. The 2005 Overview data (including trials involving a total of around 40 000 women) established clearly the efficacy of anthracycline-based adjuvant regimens in early breast cancer, and indicated an additional proportional reduction in risk of recurrence of around 11% and a proportional reduction in mortality of around 16%.[51]

✔✔ Since this Overview, other studies have confirmed the greater benefits with anthracycline-based therapy,[52–54] including, in the UK, the National Epirubicin Adjuvant Trial (NEAT).[55]

Dose of anthracyclines

The two main anthracyclines in current use are adriamycin (doxorubicin) and epirubicin. The Cancer and Leukaemia Group B (CALGB) 9344 trial randomised women with node-positive breast cancer to receive four courses of anthracycline chemotherapy to one of three different adriamycin dose levels (60, 75 or 90 mg/m^2), followed by four cycles of paclitaxel or no further chemotherapy.[55] This important dose escalation trial showed no

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benefit for adriamycin doses above 60 mg/m^2 and this dose should now be considered standard.

Cardiotoxicity is a concern with anthracyclines. Symptomatic congestive heart failure (CHF) is a rare but very serious complication in patients receiving an anthracycline-based chemotherapy regimen, with an incidence that relates to the cumulative dose received.[56,57] There is an association between the risk of cardiotoxicity and increasing age.

Anthracyclines and HER2-positive disease

Recently, the Breast Cancer International Research Group (BCIRG)-006 trial published results of a non-anthracycline regimen combined with trastuzumab, a monoclonal antibody targeting the HER2 receptor, in patients with HER2-positive early breast cancer.[58] This prospective study randomised 3222 women to one of three treatment arms: doxorubicin and cyclophosphamide followed by docetaxel (AC-T), the same regimen plus 52 weeks of trastuzumab (AC-TH), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH). Predictably, both trastuzumab-containing regimens improved DFS and OS significantly compared to the AC-T arm, but there were no significant differences between AC-TH and TCH in these outcome measures; DFS at 5 years 75%, 84% and 81% and OS 87%, 92% and 91% for AC-T, AC-TH and TCH, respectively.

Further analysis at 10 years follow-up demonstrated a sustained benefit of trastuzumab-containing regimens, with little difference in DFS and OS benefit between AC-TH and TCH chemotherapy; DFS at 10 years was 70%, 75% and 73% and OS was 79%, 86% and 83% for AC-T, AC-TH and TCH, respectively. Anthracycline-based treatments, however, resulted in significantly higher rates of cardiotoxicity and leukaemia, while the TCH regimen was better tolerated.

✔ BCIRG-006 was not designed as a non-inferiority trial, but it is reasonable to conclude that TCH is an acceptable standard of care in the adjuvant treatment of HER2-positive early breast cancer, and should be considered for those patients who have a higher baseline risk for cardiac and other toxicities.

Taxanes

Paclitaxel (Taxol) and docetaxel (Taxotere) have emerged as two of the most active cytotoxic agents against breast cancer. Several randomised trials have evaluated the benefit of taxanes combined with anthracyclines in the adjuvant treatment of early breast cancer,[59–64] but their exact role remains controversial. The majority have shown a DFS benefit, but some have failed to show a benefit in OS[59,65] or in endocrine receptor-positive tumours.[58,65] A meta-analysis of 13 randomised trials involving more than 22 000 patients assessing the addition of a taxane to an anthracycline-based regimen[66] showed an absolute improvement at 5 years of approximately 5% for recurrence and 3% for death. This benefit is present irrespective of the number of lymph nodes involved (N1–3 vs N4 +), ER status (ER positive vs ER negative) or age/menopausal status (≤50 years/premenopausal vs >50 years/postmenopausal). The most recent Oxford meta-analysis of polychemotherapy included data from 44 000 women in 33 taxane studies.[30] A significant reduction in breast cancer mortality (15–20%) was found when trials that added four separate cycles of a taxane to anthracycline chemotherapy (thereby prolonging adjuvant chemotherapy duration) were compared with anthracycline chemotherapy alone, but this benefit was much smaller (though still significant) when studies in which the number of anthracycline cycles was increased to balance treatment duration were analysed. The results of this meta-analysis suggest that the benefit from taxanes is independent of age, nodal status or hormone receptor status. It should also be noted, however, that results from the largest adjuvant taxane trial, the UK Taxotere as Adjuvant Chemotherapy Trial (TACT), involving 4162 patients, did not show a significant benefit for the addition of docetaxel to standard anthracycline chemotherapy.[65]

✔ Our interpretation of all these data is that the most convincing evidence of benefit for adjuvant taxanes is in patients with ER-negative and/or HER2-positive disease. In a retrospective analysis of the CALGB 9344 trial, in which patients with node-positive breast cancer were randomised to receive paclitaxel (175 mg/m^2) or observation after four cycles of anthracycline chemotherapy (adriamycin/cyclophosphamide, AC) at doses of 60, 75 and 90 mg/m^2,[67] patients who gained from the addition of paclitaxel were those with HER2-positive disease (including those with ER-positive and ER-negative disease) and those with HER2-negative and ER-negative disease. In contrast, patients whose tumours were HER2 negative and ER positive (by far the largest group) achieved limited benefit from the addition of paclitaxel.

Adjuvant docetaxel has also been tested instead of an anthracycline in patients with early breast cancer. In a prospective US Oncology phase III trial, a total of 1106 patients were randomised to receive either four cycles of standard AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) or four cycles of TC (docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2) as adjuvant treatment for early breast cancer.[68] Treatment with TC achieved a significant improvement in 5-year DFS compared with AC

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(86% vs 80%, respectively; HR 0.67, $P=0.015$). With further follow-up a significant overall survival benefit has also emerged.[69] There was significantly more nausea and vomiting in patients receiving AC compared with TC, whereas patients receiving docetaxel experienced more oedema, myalgia, arthralgia and a higher rate of fever and neutropenia compared with AC (5% vs 2.5%; $P=0.07$).

Which taxane and which schedule?

The optimal schedule is determined by the type of taxane selected, as demonstrated by the ECOG 1199 trial.[70] Nearly 5000 women with node-positive or high-risk node-negative disease were enrolled and received standard AC chemotherapy for four cycles, followed by paclitaxel or docetaxel, either given every 3 weeks for four cycles or weekly for 12 cycles. Progression-free survival was superior in those treated with 3-weekly docetaxel (HR 1.23), or weekly paclitaxel (HR 1.27), when compared with the standard treatment of paclitaxel given 3-weekly. Updated analysis after 10 years of follow-up demonstrated that DFS significantly improved and OS marginally improved with the weekly paclitaxel (HR 0.84, $P=0.011$ and HR 0.87, $P=0.09$, respectively) and 3-weekly docetaxel arms (HR 0.79, $P=0.001$ and HR 0.86, $P=0.054$, respectively). Exploratory analysis revealed weekly paclitaxel improved DFS and OS (HR 0.69, $P=0.010$ and HR 0.69, $P=0.019$, respectively), particularly in patients with triple-negative breast cancer.

Duration of chemotherapy

The optimum duration of chemotherapy remains uncertain. The 1998 EBCTG meta-analysis assessed five CMF-based trials and found no survival benefit for more than 6 months' treatment,[71] but the most recent data suggest that utilising chemotherapy regimens longer than four cycles of AC (more cycles or higher cumulative dose) is more effective.[30] However, data from the CALGB 40101 trial[72] showed no difference in the effect of single-agent paclitaxel compared to AC, when each was administered for four or six cycles of therapy. A French FASG-01 trial showed a significant benefit in DFS of six cycles of FEC50 over three cycles of FEC50 or 75, and improved OS with six cycles of FEC50 over three cycles.[73]

Dose density

Recently interest has developed in accelerated (also called dose-dense) chemotherapy in which treatment is given at 2-week rather than 3-week intervals with G-CSF (granulocyte colony-stimulating factor) support to overcome the risk of neutropenic sepsis. The CALGB 9741 trial has shown that accelerated 2-weekly AC×4 followed by accelerated paclitaxel×4 improved efficacy over the same eight courses given conventionally at 3-weekly intervals in women with node-positive breast cancer, with 4-year DFS of 82% and 75%, respectively.[70] In addition, the accelerated arm was associated with less neutropenic sepsis. Likewise, an Italian trial, so far presented only in abstract form, has shown a similar increase in efficacy with reduced risk of neutropenic sepsis when six courses of FEC chemotherapy were given in accelerated fashion compared with the conventional approach.[74]

Trastuzumab (Herceptin)

Trastuzumab is a recombinant humanised monoclonal antibody specific to the human HER2 receptor. HER2 is amplified in 15–20% of breast cancers. It plays a critical role in tumour development, and is an independent marker of survival with amplification or overexpression carrying an adverse prognosis.[75,76] Trastuzumab was developed as targeted therapy against HER2[77] and has established efficacy, including a significantly improved survival benefit in metastatic breast cancer.[78,79]

Four large, multicentre randomised adjuvant trials involving more than 12 000 women have assessed whether trastuzumab given concurrently with a taxane after anthracycline chemotherapy (adriamycin/cyclophosphamide, AC) (NSABP B-31; Intergroup N9831; BCIRG-006)[58,80] or concurrently with a non-anthracycline regimen of taxotere and carboplatin (BCIRG 006),[58] or sequentially after any standard chemotherapy schedule (Herceptin in Adjuvant Breast Cancer (HERA) trial)[81] or sequentially after AC and a taxane (Intergroup N9831)[82] can improve disease-free survival and overall survival (Table 15.4). In all these trials trastuzumab was given for 1 year; in the HERA trial a third arm has also evaluated treatment for 2 years (**Fig. 15.2**).

✔✔ The most recent results from these trials confirm that, with longer follow-up, there is a consistent disease-free and overall survival benefit from the addition of trastuzumab to adjuvant chemotherapy, establishing adjuvant trastuzumab as improving survival in women with HER2-positive breast cancer.[58,80,81] The hazard ratios for disease-free survival range from 0.52 to 0.76, and for overall survival range from 0.61 to 0.77, in these large trials. There was no difference in outcome for 2 years versus 1 year of trastuzumab in the HERA trial.[83]

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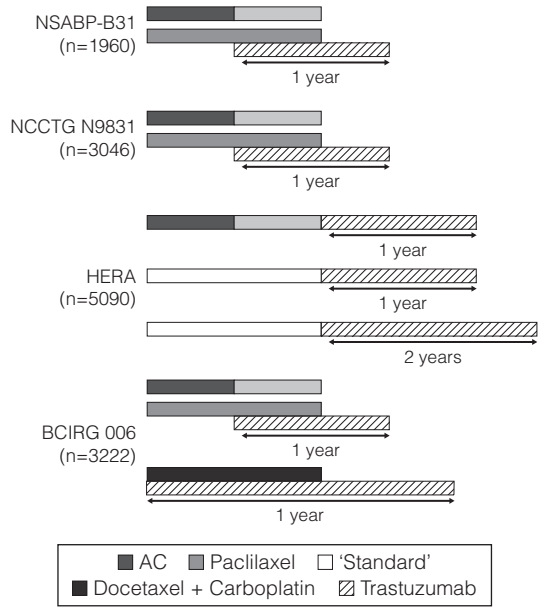

Figure 15.2 • Schematic of the main trials testing trastuzumab in the adjuvant setting.

It is worth noting that one of the early adjuvant trastuzumab trials (FinHer) found a significant improvement in DFS when only 9 weeks of trastuzumab were administered with non-anthracycline chemotherapy.[83] There was an increase in 3-year RFS compared with those receiving chemotherapy alone (89% vs 78%, HR 0.32, $P=0.02$).[70] This effect lost statistical significance with longer follow-up, but results may have been influenced by crossover in the control arm when they were first announced.[84] A number of trials continue to examine shorter durations of trastuzumab (PERSEPHONE, SOLD and PHARE) and long-term results from these studies are awaited.

Chemotherapy and trastuzumab: concurrent or sequential?

Indirect comparisons of these trials suggest improved benefit when trastuzumab is given concurrently with chemotherapy (NSABP B-31; Intergroup N9831; BCIRG-006; FinHER) rather than when it is administered sequentially (HERA) (Table 15.5). Likewise, a much smaller French PACS 004 trial involving 540 women also assessed trastuzumab given sequentially after chemotherapy and so far this is the only negative trial.[85] The inferior results of the PACS trial raise the important issue of whether trastuzumab given sequentially after chemotherapy may be inferior to concurrent administration. The definitive answer to this question comes from the N9831 trial, in which patients were randomised to control (AC followed by weekly paclitaxel, arm A), versus AC followed by weekly paclitaxel and

Table 15.5 • Adjuvant trastuzumab trials: concurrent and sequential

Trial	Treatment	Number	HR for DFS	HR for OS	Median follow-up (years)
Concurrent					
Combined US (NSABP B-31 and N9831)	NSABP: AC-T vs AC-TH N9831: AC-T vs AC-T-H vs AC-TH	3968	0.52	0.61	4
BCIRG-006	AC-T	2147	0.64	0.63	4
	TCH	2148	0.75	0.77	4
FinHER	TH-FEC vs T-FEC	232	0.65 (NS)	0.42 (NS)	5
Sequential					
HERA	Standard adjuvant chemotherapy then trastuzumab	3501	0.76	0.85 (NS)	4
PACS 004	FEC100-T Epirubicin/ docetaxel-T	540	0.86 (NS)	1.27	3

DFS, disease-free survival; HR, hazard ratio; NS, not significant; OS, overall survival.

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thereafter trastuzumab sequentially (arm B), versus AC followed by weekly paclitaxel with concurrent trastuzumab (arm C).

✔ After 6 years of follow-up, comparison of arms B and C revealed that trastuzumab given concurrently with chemotherapy resulted in a significant improvement in disease-free survival, compared to sequential chemotherapy and trastuzumab (HR 0.77).[82]

Small HER2-positive breast cancers

It is becoming clear that small (less than 10 mm) HER2-positive cancers have a worse prognosis than similarly small HER2-negative tumours.[86–88] The adjuvant trials of trastuzumab largely excluded patients with tumours of this size, but in the HERA trial patients with small (1.1–2 cm) node-negative breast cancers had a very similar benefit from the addition of trastuzumab (HR 0.53),[89] and it is reasonable to expect that this group would derive a similar reduction in risk from adjuvant chemotherapy and trastuzumab. To help address this, a US group carried out a non-randomised phase II study of single-agent weekly paclitaxel (for 12 weeks) with concurrent trastuzumab (for 1 year) in 400 patients with small HER2-positive, node-negative breast cancer. They demonstrated a risk of early recurrence of 2% in these patients over a follow-up period of 3 years when given paclitaxel and trastuzumab. This is a low recurrence rate compared to that seen in reported case series in this population, and this regimen is attractive in patients who have early breast cancer that is HER2-positive, but otherwise low risk.

Cardiotoxicity with trastuzumab

The only significant toxicity associated with trastuzumab (and one that was quite unexpected from preliminary experimental studies) is cardiotoxicity, particularly when given concurrently with or after anthracyclines. Updated cardiac safety data from three of the adjuvant trastuzumab trials were presented in 2010. Independent retrospective review of the NSAPB B-31 and N9831 trials reported that the risk of symptomatic CHF from trastuzumab was low, but that it increased from 0.45% for patients treated with chemotherapy alone to 2% when trastuzumab was added to chemotherapy.[90] The majority of patients (86.1%) experienced complete or partial recovery. A second, similar analysis of the HERA trial confirmed a low incidence of cardiac endpoints; severe CHF occurred in 0.8% vs 0% and significant decreases in left ventricular ejection fraction (LVEF) occurred in 3.6% vs 0.6% in the trastuzumab and control arms, respectively.[91] Approximately 80% of patients who suffered a cardiac event achieved 'acute recovery', defined as two or more sequential LVEF measurements of 50% or more, after the initial low ejection fraction.[91]

✔ In summary, therefore, the risk of significant and/or long-term cardiotoxicity is low with trastuzumab. There is accumulating evidence that older patients with borderline LVEF function and hypertension might be at increased risk of cardiotoxicity, and for this population it is appropriate to consider a non-anthracycline-based chemotherapy regimen in combination with trastuzumab.

Triple-negative breast cancer

Triple-negative breast cancers are defined as lacking expression of the ER, PR, and HER2 receptors.[92] They are usually associated with a high histological grade[93] and tend to have a more aggressive natural history than other breast cancer subtypes. Although sometimes considered as one group, they consist of basal, metaplastic and a heterogeneous mixture of other tumour types. Some triple-negatives express low levels of ER rather than having than no ER.

Standard adjuvant anthracycline chemotherapy results in poorer outcomes for triple-negative patients and retrospective data from CALGB 9344 suggest that triple-negative breast cancers specifically benefit from adjuvant taxanes.[67] New therapies for this subtype, including the angiogenesis inhibitor bevacizumab, are also being investigated. BEATRICE, a phase III open label study, demonstrated that addition of bevacizumab to adjuvant chemotherapy was not associated with an improved DFS in triple-negative disease; 3-year invasive DFS was 82.7% (95% CI 80.5–85.0) with chemotherapy alone and 83.7% (81.4–86.0) with bevacizumab and chemotherapy.

Two studies have examined the role of platinum therapy in the neoadjuvant setting in women with triple negative breast cancer. The German Breast Group investigated carboplatin with neo-adjuvant chemotherapy for triple-negative and HER2-positive breast cancer. Patients were randomised to receive standard neoadjuvant chemotherapy with an anthracycline/taxane combination therapy with or without the addition of weekly carboplatin. The addition of carboplatin led to an increase in pathological complete response rates in those women with triple-negative breast cancer (53.2%

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vs 36.9%, $P=0.005$). Furthermore, early survival analysis demonstrated a significant improvement in DFS in triple-negative disease; at 3 years DFS was 85.8% with the addition of carboplatin, compared to 76.1% without carboplatin; HR 0.56, $P=0.035$. However, the US CALGB 40603 study[94] showed an increased pathological complete response rate, but in this study no improvement in early DFS was observed. Ongoing translational studies are needed to identify which patients, including those with *BRCA* mutations, may benefit from the addition of platinum chemotherapy.

Bisphosphonates

Bisphosphonates are thought to alter the bone microenvironment by reducing the release of bone-derived growth factors and other modulators making the bone environment less favourable for dormant tumour cells to survive. Two of three early clinical trials indicated a benefit for the use of oral clodronate compared with placebo in the adjuvant setting in early breast cancer.[95–97] Both positive trials observed a reduction in bone metastases and improvement in overall survival. The NSABP B-34 study is the largest trial to compare clodronate with placebo in addition to adjuvant chemo- or hormone therapy. A total of 1069 patients with EBC showed that patients treated with 2 years of clodronate had a 41% reduction in the risk of developing bone metastases at 5 years ($P=0.043$) and a 23% reduction in death with a median follow-up of 5.6 years ($P=0.048$). Interestingly, the majority of patients enrolled in this trial were postmenopausal (61–64%).[98]

In contrast, the Finnish study identified a worse DFS following 3 years of adjuvant clodronate compared to placebo.[99] They enrolled 299 women with axillary node-positive breast cancer and at 10 years follow-up, DFS was significantly lower in the clodronate arm (50%) versus patients in the control arm (64%, $P=0.004$). However, postmenopausal, ER-positive women were the only subgroup not to have a negative effect from 3 years of clodronate treatment.[99]

The results of two large trials of a much more potent bisphosphonate, zoledronic acid, have been published. The Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) randomised premenopausal women with hormone receptor-positive early breast cancer to anastrazole or tamoxifen, with or without zoledronic acid.[100] All patients received goserelin for ovarian suppression. The investigators reported that disease-free survival was improved with the addition of zoledronic acid (HR 0.68), although this did not significantly affect overall survival. More recently, the AZURE trial randomising pre- and postmenopausal women to receive standard adjuvant systemic therapy with or without zoledronic acid produced complex results.[101] Overall, no difference in DFS was observed between these two groups, but in a pre-planned analysis of AZURE, postmenopausal patients (similar to the premenopausal population of ABCSG-12 who were rendered 'postmenopausal' with goserelin) had a small but significant DFS advantage, which was apparent early after diagnosis. The results of ABCSG-12 and AZURE suggest that there may be an interaction between menopausal status and the effect of bisphosphonates. This hypothesis was supported by the results of two further studies of adjuvant bisphosphonates presented in late 2011.

In an unplanned analysis of the ZO-FAST study, DFS and OS were improved by the addition of zoledronic acid to adjuvant endocrine therapy in women who were established to be postmenopausal,[102] while the GAIN (German Adjuvant Intergroup Node-Positive) study,[103] although negative overall, suggested a beneficial effect of bisphosphonates in older women.

The results of these studies led to a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) to clarify whether adjuvant bisphosphonates reduced the risk of bone and other metastases, and whether menopausal status affected efficacy. The study analysed individual patient data from 26 trials including 18 766 women (11 767 of whom were postmenopausal) with early breast cancer who were randomised to bisphosphonates or a control group with no bisphosphonate. Taking all women together, regardless of menopausal status, the meta-analyses found a highly significant reduction only in bone recurrence, and not in other breast cancer outcomes. However, subset analysis showed that the absolute reduction with bisphosphonate use in postmenopausal women at 10 years was 3.0% for breast cancer recurrence, 3.4% for distant recurrence, 2.2% for bone recurrence and 3.3% for breast cancer-related mortality. An attractive secondary gain from the use of adjuvant bisphosphonates is also the potential to reduce bone loss induced by aromatase inhibitors in this postmenopausal population. Given the favourable toxicity profile of these drugs, a change of standard practice has been advocated and the use of adjuvant bisphosphonates is being rolled out in the UK.

Emerging adjuvant therapy

Aspirin and metformin may prove to be effective adjuvant therapies, which could benefit patients worldwide and have a huge impact on cancer burden and negate the use of otherwise costly drugs on relapse. However, until the results of prospective randomised trials, such as the MA32 trial investigating adjuvant metformin and the

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ADD-ASPIRIN trial become available, these agents remain experimental as breast cancer adjuvant treatment. Targeted therapies such as Everolimus (UNIRAD trial) and PARP inhibitors (OLYMPIA trial) are also being tested in randomised trials in early breast cancer, the results of which are awaited.

Conclusion

The routine use of adjuvant systemic therapy after surgery represents an important advance in the treatment of breast cancer over the last four decades and has contributed to the improvement in breast cancer mortality.

Adjuvant endocrine therapy is indicated for all patients with hormone receptor-positive tumours. For premenopausal women with ER-positive cancers, tamoxifen remains the standard of treatment but current evidence suggests that there is additional benefit with concomitant ovarian suppression in selected patients. However, for postmenopausal women, aromatase inhibitors are the mainstay of treatment and are often used as first-line endocrine therapy in preference to tamoxifen, although the latter is still a reasonable alternative if tolerability is poor. The risk of recurrence of breast cancer is still present for at least 15 years after the initial diagnosis and there is a role for extended adjuvant endocrine therapy. This includes tamoxifen for an additional 5 years in premenopausal women, and an aromatase inhibitor after 5 years of adjuvant tamoxifen or an aromatase inhibitor in postmenopausal women.

In women with high-risk disease, and particularly in those women who have triple-negative or HER2-positive breast cancer, adjuvant chemotherapy has a key role in reducing future risk of relapse. Many patients with hormone receptor-positive disease undoubtedly also benefit, but the challenge is to define these groups more accurately using modern molecular marker technology and translational work to determine who will benefit most from chemotherapy and who might safely avoid it.

Adjuvant trastuzumab has provided a significant breakthrough for patients whose tumours amplify or overexpress HER2 receptors. Additional therapies, such as bisphosphonates and aspirin, offer further options and may expand the current armamentarium of adjuvant therapy.

Key points

- Adjuvant treatment for breast cancer after surgery is responsible for significant improvements in outcome.
- Tamoxifen remains the standard for premenopausal patients with oestrogen receptor (ER)-positive early breast cancer and an aromatase inhibitor for postmenopausal patients. Ovarian suppression should also be considered in high-risk premenopausal women.
- Adjuvant chemotherapy reduces the risk of recurrence and death from breast cancer, particularly for ER-negative and/or HER2-positive disease although absolute benefit for an individual patient may be small. A key current challenge is to identify which patients with ER-positive disease also benefit from chemotherapy.
- Adjuvant trastuzumab in addition to adjuvant chemotherapy confers a very significant benefit in patients with HER2-positive disease.
- There is a benefit for adjuvant bisphosphonates in postmenopausal women.

Full references available at **http://expertconsult.inkling.com**

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