Adjuvant Systemic Treatment for Breast Cancer: An Overview

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It has long been recognized that breast cancer is not always cured by loco regional treatment alone. To reduce the risk of local and distant recurrence, patients are usually offered adjuvant systemic treatment. The aim of adjuvant systemic therapy is thought to principally be elimination of clinically undetectable micrometastatic disease. The decision to offer this treatment is based on the estimated five- and ten-year risks of recurrence-free survival and overall survival. This risk is estimated using pathological factors such as tumour size, grade of tumour, receptor status, nodal involvement and biological factors such as patient age and co-morbidities along with a multidisciplinary recommendation. The estimated benefits must be balanced against the acute and chronic toxicities of the proposed treatment and an informed decision made with the patient. Increasingly, multi-parametric tests such as Oncotype Dx or MammaPrint are also used to help in this decision process. Systemic treatment includes the use of endocrine therapy, chemotherapy, antibody treatment, and more latterly immunotherapy.

18.1 Aims of Adjuvant Therapy

18.1.1 Micro-Metastatic Disease

The main aim of adjuvant systemic therapy is thought to be the eradication of micro-metastatic disease which otherwise is the cause of relapse in the future. Studies have shown that cancer cells can lie dormant for many years despite radical treatment and cause recurrent disease which is often metastatic by the time it is diagnosed. The difficulty is "proving" who has residual disease when there is no way clinically of detecting it. Understandably, this can be a difficult concept for patients to understand. Currently there is no gold standard algorithm or molecular test to determine the need or not of adjuvant treatment, but the chance of relapse is estimated using the aforementioned prognostic features, individualized to each of the patients. Inevitably by this selection process, some patients will receive chemotherapy inappropriately, gaining no survival benefit, but potentially suffering acute and chronic side effects from the treatment. Even if we could prove that an individual patient did have micro-metastatic disease, could we then prove the treatment will work? Some patients will have chemorefractory or resistant disease and again go through months of unnecessary treatment. Resistance can be acquired or intrinsic to the cancer and this is explained by the molecular complexity of tumours and intramural heterogeneity. Genetic mutations, the microenvironment and the presence of cancer stem cells all enable tumours to develop resistance [1].

18.1.2 Cancer Stem Cells

Cancer stem cells were first demonstrated in haematological malignancies but now are recognized in solid tumours such as breast cancer [2]. Cancer stem cells are able to self-heal, reproduce endlessly and randomly mutate leading to tumour heterogeneity, which is what makes treatment complex [2]. There is some evidence that traditional chemotherapy targets the tumour bulk but not the cancer stem cells, which can produce new clones resistant to treatment. Ongoing studies to evaluate efficacy of targeted molecular therapies to cancer stem cells is a challenging but promising development in the treatment of cancer.

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18.1.3 Immunogenicity

Immunogenic cancers such as melanoma have been proven to innately initiate an anticancer T-cell response that can result in tumour death. Due to genetic alterations, cancer cells have many different antigens present in their cell surface [3]. These lead to binding of peptides with major histocompatibility complex class 1 (MHC1) which distinguish cancer cells from normal cells. These complexes can be recognized by CD8 + T cells which are produced in cancer patients [4]. This could lead to immunity or cell death but infrequently does. Many ways of trying to exploit this natural response including vaccines, immune checkpoint therapy and monoclonal antibodies have all gained FDA approval. Based on the success seen in melanoma, trials have been quickly established to evaluate efficacy in other solid tumour types. Breast cancer was long thought to be non–immunogenic; however, many studies have now established that the presence of CD8 + T cells—particularly in the HER2+ and triple negative groups—does translate into a reduction of relative risk of death from the disease [5–8]. Whilst not the current focus of adjuvant systemic treatment in breast cancer, the use of immunotherapy for all solid tumour types is likely to expand into the adjuvant setting over the next few decades.

18.2 Adjuvant Chemotherapy: The Evidence

Over the years many, trials have been done to try and establish the optimal drug or drug combinations, doses and duration of adjuvant chemotherapy. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was set up in the mid-1980s with the aim of performing a systematic review of all existing randomized control trials every five years in order to provide the most comprehensive evidence base [9].

18.2.1 Single Agent or Combination Chemotherapy

Adjuvant cytotoxic chemotherapy in breast cancer began with trials of single alkylating agents which then led to trials of combination therapy with anthracyclines and taxanes. Prior to this radical surgery was the gold standard; however, subsequent trials showed that distal recurrence remained a huge issue despite initial radical surgery [10, 11]. The National Surgical Adjuvant Breast Project (NSABP) was the organization behind the first trial to report in 1968 that the alkylating agent thiotepa reduced risk of recurrence after radical surgery in pre-menopausal node positive patients [12]. Similarly, the alkylating agent L-Phenylalanine mustard that had been developed during the Second World War was found to have similar efficacy in reducing disease recurrence when given adjuvantly [13].

Combination chemotherapy in breast cancer was first explored in the 1960s [14]. Cyclophosphamide, methotrexate and 5-fluorouracil (CMF) was the first combination to be trialled for adjuvant breast cancer patients at Istituto Nazionale Tumori in Milan, Italy, with increasingly positive results [15]. Initially the trials targeted node positive pre-menopausal women but as they expanded similar positive results were found in postmenopausal and/or node negative patients [16, 17]. Subsequently, six cycles were found to be as effective as 12 cycles of adjuvant CMF [18].

18.2.2 Anthracyclines

Anthracyclines were initially introduced to try and reduce the duration and emetogenis of the classical CMF regimen. The first widely used regime was doxorubicin and cyclophosphamide (AC). Although there was no apparent advantage in efficacy over CMF [19], thus started the era of trials to find the most efficacious adjuvant regime. In 2001, the National Institute of Health recommended adjuvant chemotherapy as standard practice in locally advanced breast cancer patients [20].

The first meta-analyses of combination chemotherapy (focusing mainly on anthracycline regimes) were done by the EBCTCG in 2005 [21]. They included 194 randomized trials with a total of almost 150,000 patients. From their analyses, there was clear evidence that single agent chemotherapy regimens reduced rates of recurrence; however, combination treatments reduced not only recurrence, but also mortality [10]. Not separating the data for age, the annual rates of recurrence were reported as 0.86 for single agents and 0.77 for combination. Mortality reductions rates were 0.96 for single agents and 0.83 for combination [21].

With both single agent and combination chemotherapy, there were greater benefits established in the younger population (<50 years old) but both for recurrence and mortality the age standardized effects of single versus combination regimens were superior for combination treatments [21]. Of note (as is common in trial populations), there were few patients included aged >70 years.

Figure 18.1 shows the 15-year recurrence and mortality rates split into age groups of <50 and 50–69, all of which show a statistically significant ($2p < 0.00001$) benefit with adjuvant combination regimens [21].

For women aged <50, the absolute 15-year reduction in recurrence-free survival (RFS) was 12.3 % with a 10 % reduction in mortality. In women aged 50–69, the 15-year benefits for RFS and mortality were more modest at 4.1 and 3 %, respectively. This benefit remained significant regardless of axillary lymph node involvement, so this may not be

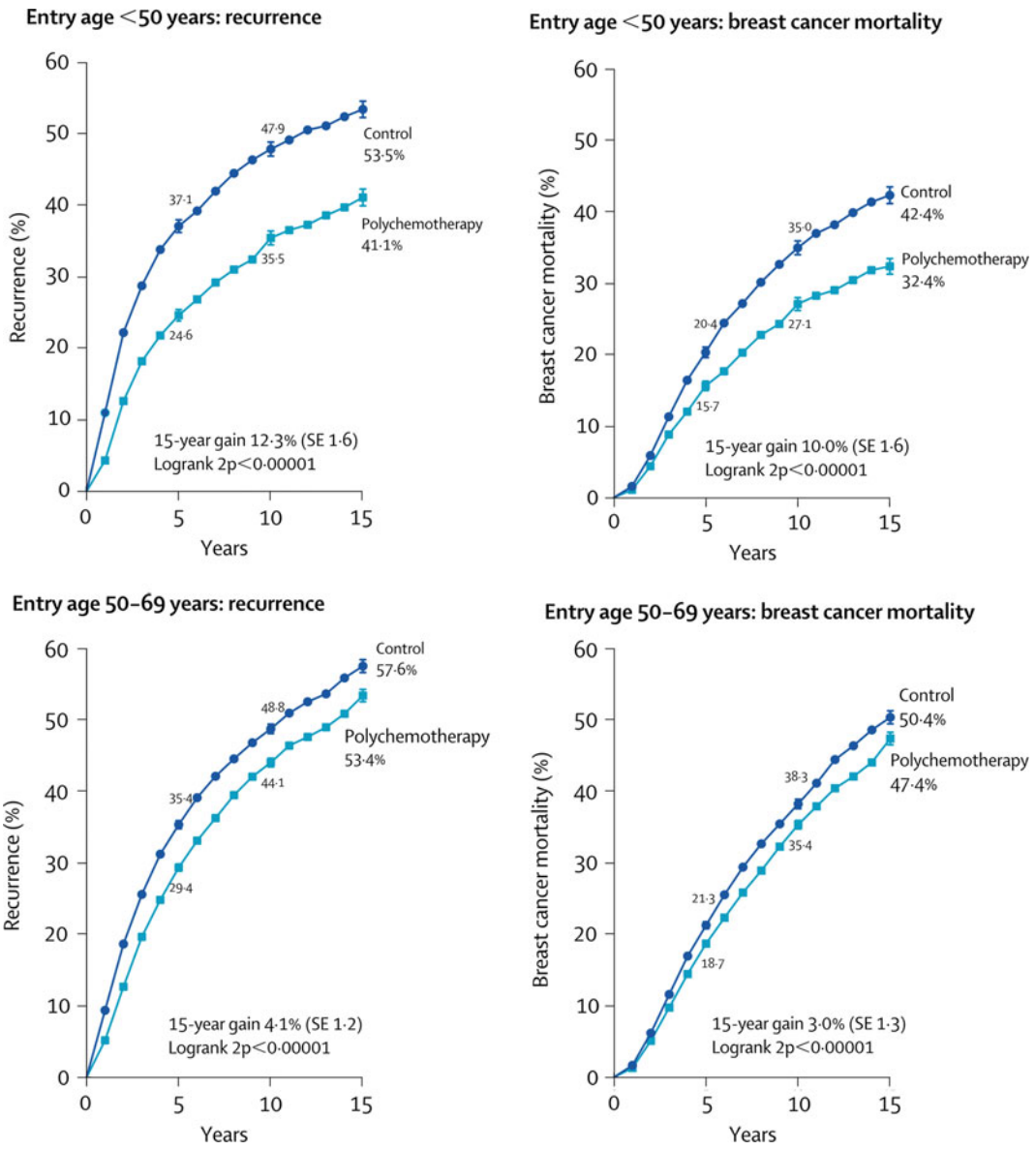

Fig. 18.1 Polychemotherapy versus not, by entry age <50 or 50–69: 15-year probabilities of recurrence and of breast cancer mortality. Younger women, 35 % node positive; older women 70 % node positive. Error bars are 1SE. Reprinted from The Lancet, Vol. 365, Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials, pp. 1687–1717, © 2005, with permission from Elsevier

of relevance to the proportional reduction in either age group. For the women aged <50, the 5-year gains in RFS were 9.9 % ($2p < 0.00001$) for node negative patients and 14.6 % ($2p < 0.00001$) for node positive. For the age group 50–69 and node negative, the 5-year RFS improvement was 5.3 % ($2p < 0.00001$) and 5.9 % ($2p < 0.00001$) for node positive patients [21].

Separating the data for age and ER status showed the greatest benefit in RFS was in ER poor patients when treated with adjuvant chemotherapy. For women <50 with ER poor tumours (20 % node positive), RFS improvement at 5 years was 13.2 % ($2p < 0.00001$) and for the same age group but ER positive (34 % node positive) it was 7.6 % ($2p < 0.00001$). For the age group 50–69 who were ER poor (66 % node positive), RFS gain at 5 years was 9.6 % ($2p < 0.00001$) and for the same age group ER positive (73 % node positive) RFS improvement was 4.9 % ($2p < 0.00001$) [21]. In the ER positive group, the arms were combination chemotherapy plus tamoxifen versus tamoxifen alone for both age groups.

For the CMF regimen trials, duration of treatment varied from 6, 9 or 12 months with no statistical difference being observed for longer treatment. The anthracycline-based trials on average had a treatment duration of 6 months but they did

change between doxorubicin and epirubicin as the anthracycline used (FAC or FEC) [21].

For ER positive women with breast cancer aged <50, anthracycline regimens studied in this meta-analyses reduced the annual mortality rate by 38 % and for women aged 50–69 by 20 %. This does not include, but added to, the additional benefit of adjuvant endocrine therapy which will be evaluated later in this chapter. These results were significantly more effective than CMF regimens ($2p = 0.0001$ for both recurrence and $2p < 0.00001$ mortality) [21].

In 2008, the EBCTCG published a further view of combination chemotherapy in ER poor patients who appeared to be the subset gaining the biggest survival advantage from adjuvant combination chemotherapy [22]. Ninety-six trials were included in this meta-analysis. In women <50 years old, the 10-year reduction in RFS with the addition of chemotherapy was 12 % ($p < 0.00001$) and reduction in mortality was 8 % ($p = 0.0002$). In women aged 50–69, the 10-year reduction in RFS with the addition of adjuvant chemotherapy was 10 % ($p < 0.00001$) and reduction in mortality was 6 % ($p = 0.0009$) [22].

In 2011, EBCTCG published further analyses of overall survival for adjuvant CMF versus no adjuvant chemotherapy. Adjuvant CMF reduced the risk of recurrence by 30 % at 10 years ($p < 0.0001$) which translates to an absolute gain of 10.2 %. The 10-year mortality was reduced by 16 % ($p < 0.0004$) which translates to an absolute gain of 4.7 % at 10 years [23].

An alternative regimen was to incorporate an anthracycline into the classical CMF treatment which was known as a block-sequential design. Bonadona et al. were the first to use this in a trial of women with breast cancer with more than three positive lymph nodes. They either received sequential doxorubicin then CMF or alternating cycles of doxorubicin and CMF. OS at ten years was 58 % in the sequential arm versus 44 % in the alternating arm ($p = 0.002$) favouring sequential sequencing [24]. The NEAT trial allocated four cycles of epirubicin followed by four cycles of CMF (E-CMF) and in 2008 reported a 28 % benefit for RFS and 30 % advantage in OS compared to standard CMF alone [25]. Overall toxicity in the E-CMF arm was low but unsurprisingly higher than the CMF alone arm. Interestingly, more deaths during treatment occurred on the CMF arm and any deaths on the ECMF arm all occurred during CMF administration [25].

18.2.3 Taxanes

In the 1970s, taxanes became the first new cytotoxic drugs to be developed for decades. Having been shown to be of value in the metastatic setting, the next step was to establish if they would add to the efficacy of adjuvant chemotherapy [26].

Concurrent administration of doxorubicin and paclitaxel enhanced the effect of the anthracycline rendering the regimen too cardiotoxic [27]. Theories suggested that sequential administration may be preferable and result in more anti-tumour activity [28, 29]. Docetaxel, however, does not effect the pharmacokinetics of doxorubicin.

In the CALGB 9344 trial which escalated doses of doxorubicin in combination with cyclophosphamide followed by 4 cycles of paclitaxel in node positive patients, RFS (HR 0.83 $p = 0.0023$) and OS were improved (HR 0.82 $p = 0.006$) [30].

In the NSABP B-28 trial, an additional 4 cycles of paclitaxel after 4 cycles of doxorubicin and cyclophosphamide (AC) in node positive patients improved RFS but not OS [31]. These two trials differed in trial design as the CALGB 9344 trial gave endocrine therapy after completion of chemotherapy, whereas NSABP B-28 gave it concurrently [32].

As part of the same review in 2011, the EBCTCG meta-analysis reviewed the addition of taxanes to combination chemotherapy to address the question of how much benefit could be gained. Treatments varied by the taxane used (paclitaxel or docetaxel), dose and schedule (3 weekly or weekly). All but two trials compared a taxane plus anthracycline regimen to an anthracycline control arm. The results were grouped into those which added four extra cycles of a taxane to a standard regimen or those which gave the same duration of chemotherapy in all arms [23].

In the trials which gave additional cycles of a taxane after a standard regimen, RFS over 8 years was reduced by 4.6 % ($2p < 0.00001$) and OS by 3.2 % ($2p = 0.0002$), whereas in those trials that tested the benefit of additional taxanes but without prolonging the duration of therapy, the improvement in RFS at 5 years was by 2.9 % ($2p < 0.00001$) and for OS it was 1.2 % ($2p = 0.008$) [23].

AC has also been directly compared to docetaxel and cyclophosphamide (TC) by the US oncology research group. This is one of the few trials that included an arm with no anthracycline. With an average follow-up of 84 months, RFS (HR 0.74 $p = 0.033$) and OS (HR 0.69 $p = 0.0032$) were improved in the TC arm. These data suggest we should consider taxane only therapies as a suitable alternative, especially amongst those patients who may have pre-existing cardiac issues [33, 34].

As mentioned earlier, docetaxel does not have the same pharmacokinetics as paclitaxel when given concurrently with doxorubicin. Trials have compared docetaxel, doxorubicin and cyclophosphamide (TAC) to FAC. The Breast Cancer International Research Group (BCIRG) trial 0001 and GEICAM 9805 saw a definite benefit in RFS (28 % in BCIRG 001) and a trend towards improved OS (BCIRG 0001 did demonstrate a statically significant improvement in

OS but GEICAM did not) [35, 36]. TAC was, however, undoubtedly more toxic in both trials.

So far the question has not been answered as to whether it is the addition of the taxane that improves outcomes or the prolonged duration of adjuvant chemotherapy. PACS01 compared 6 3-weekly cycles of FEC to 3 3-weekly cycles of FEC followed by 3 3-weekly cycles of docetaxel in 1999 node positive patients [37]. RFS (HR 0.85 $p = 0.036$) and OS (HR 0.75 $p = 0.007$) were improved in the taxane arm with median follow-up of 93 months [38].

The UK TACT study also included high-risk node negative patients and had over 4000 patients in the study to ensure it was sufficiently powered. Each arm was extended to include 8 cycles of treatment. The randomization was between a research arm of 4 3-weekly cycles of FEC followed by 4 3-weekly cycles of docetaxel versus control arm of physicians' choice of 8 3-weekly cycles of FEC or 8 3-weekly cycles of E-CMF. No statistical difference was found between either arm after 62 months of follow-up [39].

Chemotherapy can be given in fixed doses at fixed intervals or as smaller doses on a more frequent basis (dose dense regimen). The ECOG E1199 trial was designed to answer whether sequential dose dense taxane administration was superior to a 3-weekly regime [40]. There was no superiority seen between docetaxel and paclitaxel given 3 weekly or weekly, respectively. RFS (HR 0.73 $p = 0.0006$) and OS (HR 0.68 $P = 0.01$) were superior, however, when paclitaxel was given weekly over 12 weeks as opposed to 3 weekly for 4 cycles. [40] The final analysis after 12.1 years of follow-up showed that RFS and OS were improved for weekly paclitaxel (HR 0.84 $p = 0.011$ and HR 0.87 $p = 0.09$) and 3-weekly docetaxel (HR 0.79 $p = 0.001$ and HR 0.86 p = 0.054) in comparison with the standard arm of 4 cycles of 3-weekly paclitaxel [41].

18.3 Adjuvant Endocrine Therapy

It is widely acknowledged that the only patients to gain benefit from adjuvant endocrine treatment are those who have oestrogen receptor (ER) positive breast cancer [42]. The EBCTCG meta-analyses concluded that there was a significant reduction in rate of recurrence and breast cancer mortality when ER positive patients were given 5 years of tamoxifen. This was a clearer benefit than was seen in earlier studies where patients had only been given 1–2 years of tamoxifen [21]. For these women, the annual rate of recurrence was halved and breast cancer mortality reduced by a third. Most of the effect on recurrence is in those 5 years whilst on treatment but the effects on mortality last beyond this time period.

The 15-year gain in patients with ER positive disease after 5 years of tamoxifen for recurrence is 11.8 % ($2p < 0.00001$) and 9.2 % ($2p < 0.00001$) for breast cancer mortality [21]. The risk reduction appears to be independent of patient age, nodal status or whether the patient received adjuvant chemotherapy. The absolute risk reduction is similar in all age groups but is more significant in the node positive population [21].

The NSABP B-14 trial randomized ER positive, node negative patients to five years of tamoxifen versus 5 years of placebo. 10-year follow-up showed improved RFS (69 % vs. 57 % $p < 0.0001$) and OS (80 % vs. 76 % $p = 0.02$) [43]. Again these results were consistent regardless of age and also showed a reduction in the risk of contra-lateral breast cancer (4.0 % vs. 5.8 % $p = 0.007$) [43]. Attempting to address the question of optimum duration of adjuvant endocrine therapy, participants at the end of the trial who had received tamoxifen (and were alive with no recurrence) were randomized to a further 5 years of tamoxifen or 5 years of placebo [43]. Results showed no additional benefit and in fact favoured stopping after 5 years. RFS was 82 % for the placebo group versus 78 % ($p = 0.03$) and OS was 94 % for the placebo group and 91 % for ten years tamoxifen ($P = 0.07$) [44]. These data seemed to support stopping adjuvant endocrine therapy at 5 years; however, subsequent larger trials showed this to be erroneous.

In the ATLAS trial, 12 894 women were randomized to 5 or 10 years of adjuvant tamoxifen. There results show a survival benefit for 10 years of adjuvant treatment which even extended past the 10-year point of stopping treatment [45]. The cumulative risk of recurrence years 5–14 was 21.4 % for those on 10 years of tamoxifen versus 25.1 % control group. Mortality rates from breast cancer years 5–14 were 12.2 and 15 %, respectively. That equals an absolute mortality reduction of 2.8 % [45].

In the aTTom study, women continuing tamoxifen for 10 years had a 25 % lower recurrence rate and a 23 % lower breast cancer mortality rate compared to those who stopped at 5 years. Non-breast cancer mortality was not significantly affected but there were increased incidences of endometrial cancer [46].

18.3.1 Aromatase Inhibitors

The ATAC trial compared the aromatase inhibitor (AI) anastrazole to tamoxifen in postmenopausal women each taken for five years. RFS was improved in the ER positive group who received anastrazole (HR 0.86 $p = 0.003$) but there was no statistical significance in OS. The benefit persisted past the initial 5 years. When further analysed, the greatest benefit was seen in those patients who were ER positive but PGR negative. Whilst on active treatment the risk of fractures was higher in the group receiving AI but after discontinuation there was no difference in risk between groups. Interestingly, however,

treatment-related serious adverse events were more common in the tamoxifen arm whilst on active treatment [47]. The BIG 1–98 trial also confirmed RFS was significantly improved in the postmenopausal women randomized to letrozole who had ER positive tumours (HR 0.82 $p = 0.007$) [48].

This led to aromatase inhibitors being recommended as standard adjuvant treatment in many/most postmenopausal women with ER positive breast cancer.

The ARNO 95 study looked at whether postmenopausal ER positive women could gain benefit after 2 years of tamoxifen by switching to the AI anastrazole. RFS (HR 0.66 $P = 0.049$) and OS (HR 0.53 $P = 0.045$) were improved by switching to the AI [49]. This showed RFS is improved for the postmenopausal ER positive subgroup either by having an AI as their standard treatment or sequentially post-tamoxifen.

Similar results were shown with the steroidal AI exemestane with RFS (HR 0.76 $p = 0.0001$) in the intergroup exemestane study [50].

The National Institute of Canada (NCIC) MA17 trial evaluated the efficacy of adding five years of letrozole after completing 5 years of tamoxifen compared to placebo [51]. For node negative patients and node positive patients, RFS was improved (HR 0.47, HR 0.60, respectively). In the node positive subset, this was the first time a benefit in OS had been demonstrated with letrozole (HR 0.61). Most benefit seemed to be in the ER+/PGR+ subset although this was a subset analysis [52].

Based on these trials, current ASCO guidelines recommend that women who have hormone receptor positive breast cancer and are pre- or peri-menopausal after 5 years of adjuvant tamoxifen should be offered to extend treatment to a total of 10 years [53]. If they are postmenopausal, they should be offered the choice of continuing tamoxifen or switching to an aromatase inhibitor to complete ten years of adjuvant endocrine therapy [53]. What remains unknown, although trial results are awaited, is the optimum strategy after 5 years' aromatase inhibition: whether further endocrine therapy is effective, and if so which is optimal, tamoxifen or continued aromatase inhibition.

18.4 Monoclonal Antibodies

Over expression of HER2/neu oncogene occurs in 15–20 % breast cancers and has prognostic implications with shorter RFS and OS [54]. Trastuzumab is a humanized monoclonal antibody against HER2 which has been proven to improve survival for this subset of patients. It does have a risk of cardiac toxicity which is amplified when combined with anthracyclines which form the base of many adjuvant regimens so the risk/benefit ratio has to be evaluated in the adjuvant population.

The NSABP-31 trial and N9831 trial were designed to evaluate the efficacy of adjuvant trastuzumab in node positive HER2 positive breast cancers. The NSABP-31 trial compared doxorubicin and cyclophosphamide followed by 3-weekly paclitaxel versus the same regimen with the addition of trastuzumab with the 1st paclitaxel dose continuing for 52 weeks. N9831 had an additional arm where trastuzumab was given sequentially for 52 weeks after completing paclitaxel [55]. As the two trials were similar in design, joint statistical analysis was performed to derive the estimated survival benefit. The relative improvement in OS was 37 % (HR 0.63 $p < 0.001$) giving an 8.8 % increase in OS at 10 years. RFS was also improved with a relative reduction of 40 % (HR 0.60 $p < 0.001$) and an increase in 10-year RFS 11.5 % [55].

Subsequent analyses evaluated cardiac function in node positive HER2 patients who had completed surgery and were either allocated to AC and then 3-weekly paclitaxel or the same regime but adding trastuzumab concurrently with the paclitaxel cycles. Overall there was a 4.1 % incidence of class III or IV congestive heart failure (CHF) and an overall incidence of any degree of CHF of 19 % [56].

The standard of care has been 1 year of antibody therapy. The HERA trial looked at whether survival could be improved with longer treatment duration, so it additionally compared 1 versus 2 years of trastuzumab to observation only, with all trastuzumab being commenced after completion of the chemotherapy. Severe cardiac toxicity was lower in the HERA trial than in the North American trials where the trastuzumab was commenced 3 weeks after the last dose of anthracycline and was similar at around 1 % in the 1- and 2-year arms. However, less severe cardiac toxicity was higher in the arm who received 2 years of treatment but with no improvement in DFS or OS. As expected, 1 year of trastuzumab was better than observation with DFS (HR 0.76 $p < 0.001$) and OS (HR 0.76 $p = 0.0005$) [57].

There are ongoing studies to evaluate whether 6 months of treatment may be adequate and reduce the incidence of cardiac toxicity. Preliminary data from the PHARE trial suggest 12-month treatment is superior so this still remains standard of care [58]. The Fin Her study (which was a much smaller trial) allocated patients to docetaxel or vinorelbine for 3 cycles followed by 3 FEC and then the HER2 positive patients were randomized to 9 weeks of trastuzumab [59]. Interestingly, RFS was improved even after 9 weeks of treatment from 78 % to 89 % after three years [59].

The BCIRG 006 study tested for HER2 status by FISH amplification in all patients, and like HERA, also included node negative patients [60]. It compared AC and docetaxel (T) trastuzumab (H) with, on the one hand, docetaxel and carboplatin and trastuzumab (TCH), and on the other hand, AC–T. RFS at 5 years was significantly better in the

trastuzumab arms—AC–T 75 %, AC–TH 84 % and TCH 81 %. The rates of cardiac toxicity were higher in the anthracycline and trastuzumab arms [60].

18.5 Adjuvant Bisphosphonates

Bisphosphonates have been used in the metastatic setting to treat hypercalcaemia, bone pain and reduce fracture incidence for many years; however, there is increasing evidence that they may be of value in the adjuvant setting. The ABCSG-12 and AZURE trials generated the hypothesis that menopausal status might be the biggest predictor of response to adjuvant bisphosphonates with bone recurrence and breast cancer mortality being reduced in those who were postmenopausal or undergoing ovarian suppression [61, 62]. Previous trials in this area have mixed results but a subsequent individual patient meta-analysis of over 18,000 patients by the Early Breast Cancer Trialist's Collaborative Group provided level one evidence of a bisphosphonate class effect when used in this indication [63]. The meta-analyses included data on 18,766 women from 24 trials. In all women, regardless of menopausal status there was a definite reduction in bone recurrence RR 0.83, 95 % CI 0.73–0.94; $2p = 0.004$. Subanalysis amongst postmenopausal women showed a reduction in overall recurrence RR 0.86, 95 % CI 0.78–0.94; $2p = 0.002$, distant recurrence RR 0.82, 95 % CI 0.74–0.92; $2p = 0.003$, bone recurrence RR 0.72, 95 % CI 0.60–0.86; $2p = 0.0002$ and breast cancer mortality RR 0.82, 95 % CI 0.73–0.93; $2p = 0.002$. Another important effect was the significant reduction in bone fractures (RR 0.85, 95 % CI 0.75–0.97; $2p = 0.02$) [63].

The absolute gain from treatment at 10 years was 3.3 % for breast cancer mortality (95 % CI 0.8–5.7) and 2.2 % for bone recurrence (95 % CI 0.6–3.8). This was independent of ER status, nodal involvement, grade of tumour or concomitant chemotherapy. There was also no significant effect of class of bisphosphonate used or duration of treatment [63]. Despite these data, the use of adjuvant bisphosphonates as standard of care remains controversial and is not a licensed/approved use of these agents.

18.6 Ovarian Suppression

Ovarian ablation as a treatment in breast cancer was first published by George Beatson in the Lancet in 1896 [64]. Although at that time the mechanism was not well understood it remains an integral part of treatment in the modern setting. Nowadays surgical castration is not always needed given the advent of chemical suppression by gonadotropin-releasing agonists which results in down-regulation of oestrogen production.

In 1996, the EBCTCG published an overview in the Lancet of the randomized trials of those allocated to ovarian ablation with the addition of long-term follow-up data. From over 2000 women <50 years old, 15-year survival was increased amongst those who received ovarian ablation (52.4 % vs. 46.1 % $2p = 0.001$) as was RFS (45 % vs. 39 % $2p = 0.0007$). The benefit was independent of nodal status but did appear smaller in those women who received chemotherapy as well as ovarian ablation [65].

In meta-analyses of 11 906 premenopausal women across 16 randomized control trials, LHRH agonists as single adjuvant therapy did not significantly reduce recurrence or death [66]. Combination with tamoxifen, chemotherapy or both reduced risk of recurrence by 12 % ($p = 0.02$) and death by 15.1 % ($p = 0.03$) and LHRH agonists were ineffective in hormone receptor negative cancers. LHRH agonists showed similar efficacy to chemotherapy as there was no significant difference when comparing the two arms for recurrence (HR 1.04 $P > 0.25$) or death (HR 0.89 $p > 0.37$). It is important to note, however, that none of the studies included taxanes so it can only be concluded that LHRH efficacy is similar to that of anthracycline-based systemic treatment [66].

We have established that adjuvant therapy with an AI improves outcomes in postmenopausal women with ER positive breast cancer. If ovarian function could be suppressed, would premenopausal women get enhanced benefit from an AI rather than tamoxifen? The TEXT and SOFT trials set out to investigate this randomizing ER positive premenopausal woman to the AI exemestane with ovarian suppression versus tamoxifen with ovarian suppression for a period of five years [67]. Ovarian function could be switched off chemically using gonadotropin-releasing hormone agonist triptorelin, surgically with oophorectomy or with ovarian irradiation. DFS was 91.1 % at 5 years in the group who got an AI + OS and 87.3 % with tamoxifen + OS. OS did not differ significantly and adverse events were similar in both arms [67].

18.7 Genomic Testing

There are several genomic tests for breast cancer and the most validated of these is Oncotype Dx. This analyses the expression in the primary tumour of 21 genes using reverse transcription polymerase chain reaction (RT-PCR) on RNA isolated from paraffin-embedded breast cancer tissue, generating a score for risk of recurrence which aids clinicians and patients in their decision as to whether they should pursue adjuvant systemic therapy. A low score predicts

better outcomes, with some evidence that this group of patients' gains little additional benefit from adjuvant chemotherapy. It is thus prognostic and also estimates the likelihood of response to chemotherapy, thus avoiding chemotherapy in those patients who would receive no clinical benefit [68]. In a retrospective planned analysis of 367 specimens in ER positive, node positive postmenopausal women (SWOG 8814 trial which showed survival benefit for adjuvant cyclophosphamide, doxorubicin and fluorouracil (CAF) prior to tamoxifen), the recurrence score was prognostic in the tamoxifen alone group ($p = 0.006$; hazard ratio [HR] 2.64, 95 % CI 1.33–5.27, for a 50-point difference in recurrence score). There was no benefit of CAF if patients had a low recurrence score regardless of nodal involvement (<18; log-rank $p = 0.97$; HR 1.02, 0.54–1.93) but an improvement in RFS for a high recurrence score adjusting for the number of positive nodes (score > or = 31; log-rank $p = 0.033$; HR 0.59, 0.35–1.01) [68]. Oncotype Dx is included in the American Society of Clinical Oncology and National Comprehensive Cancer Network, ESMO and St Gallen guidelines as an adjunct to clinician decision-making regarding adjuvant chemotherapy [69–72].

The MammaPrint assay uses microarray technology to analyse a 70-gene expression profile to identify those at risk of developing metastatic disease [73]. This test was used on T1 tumours to identify how many would be at risk of distant recurrence without adjuvant treatment. The MammaPrint signature was an independent prognostic factor for breast cancer-specific survival (BCSS) at 10 years (HR 3.25 $P < 0.001$) and predicted distant disease-free survival (DDFS) at 10 years for 139 patients with T1a/b cancers (HR 3.45 $p = 0.04$) [74].

In a study designed to assess the predictive value of the MammaPrint assay for adjuvant chemotherapy prior to endocrine treatment, results were pooled from study series [75]. The test classified 253 patients as low risk and 289 as high risk. In the low-risk group, BCSS at 5 years was 97 % for the group on adjuvant endocrine therapy and 99 % for those allocated adjuvant chemotherapy prior to endocrine therapy (HR 0.58 $p = 0.62$). DDFS was 93 % versus 99 % (HR 0.26 $p = 0.20$). In the high-risk group, BCSS was 81 and 94 %, respectively, at 5 years (HR 0.21 $p < 0.01$) and DDFS was 76 % versus 88 % (HR 0.35 $p < 0.01$). This estimates significant survival benefit from adjuvant chemotherapy in the high-risk patients and no significant benefit in the low-risk patients [75].

The prospective RASTER study reported those classified as low risk by the MammaPrint assay (of whom 85 % did not receive adjuvant chemotherapy) had a 5-year distant-free recurrence of 97 % [76]. The FDA has approved the MammaPrint signature to help evaluate whether patients are deemed low or high risk but not to estimate their benefit from adjuvant chemotherapy.

The Prediction Analysis of Microarray 50 (PAM50) generates a risk recurrence score to predict prognosis in ER positive postmenopausal women by separating intrinsic breast cancer subtypes (luminal A, luminal B, HER2 positivity and basal-like). In a study comparing PAM50 with Oncotype Dx, more patients were scored high risk and fewer as intermediate risk by PAM50, suggesting it provided more prognostic information and better differentiation between high- and intermediate-risk patients [77].

So, should intermediate-risk patients still get adjuvant chemotherapy? The TAILORx trial is attempting to answer this question by randomizing those calculated as being intermediate risk to chemotherapy or not. The study is prospectively testing the use of Oncotype Dx to select for patients who can avoid chemotherapy [78]. So far results have only been released for the low-risk group, in which their good prognosis without chemotherapy has been confirmed [79].

The MINDACT trial is comparing the 70-gene signature with the pathological factors we commonly use to make clinical decisions regarding adjuvant chemotherapy. Again this is looking at those deemed intermediate risk and also further evaluating the predictive effect of the MammaPrint assay [80].

This is clearly an evolving area and one that is likely to dramatically influence clinical practice and decision-making over the next few years. So far all of these tests seem to be good prognostic tools but what has not yet been proven is their ability to safely identify patients who do not need chemotherapy. So far no single test has been validated as superior to the others available on the market.

18.8 Trials in Older Patients

An area that is beginning to be explored is incorporating or designing trials where the aim is to establish efficacy in the over 70 population. Many patients now fall into this age category and are fit for systemic treatment; however, we have little evidence of the efficacy of these drugs in this population. Historically, there has been reluctance to include this cohort in trials given potential co-morbidities, decline in organ function and perceived increased susceptibility to toxic side effects. The few studies that have included older women found a comparable incidence of complications in women both older and younger than 65 years of age [81–83]. These older patients, however, appear to have been selected by fitness and their lack of other health problems meaning they do not truly represent the older population as a whole. Hardly any of these trials have included women over 80 meaning we have no reliable information regarding tolerability or efficacy in this cohort [84]. There is increasing thought that geriatricians should be involved from the initial

oncology consultation to perform a comprehensive geriatric assessment to aid the decision process and allow adjustments for age-related co-morbidities [85].

The data reviewed in this chapter clearly show that patients' outcomes are improved with adjuvant systemic treatment. The choice of which therapy or combinations of therapies to use depends on the tumour biology, patient characteristics and an evaluation of the relative benefits and deficits.

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