Standard medical treatment for early breast cancer

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Introduction

For the first time since the introduction of systemic adjuvant therapy, a decline in breast cancer-associated mortality is becoming apparent in the Western world. Although detection of cancer at earlier stages with screening mammography probably accounts for some of this mortality reduction, it is clear from the Oxford overviews of adjuvant therapy, that both chemotherapy (CT) and tamoxifen play significant roles in preventing relapse and death from breast cancer. Their effects are additive, and the magnitude of benefit varies depending on several tumour and patient characteristics, factors which help individualise therapy and maximise the benefit harm ratio. In an attempt to improve upon these gains, ongoing randomised trials are exploring new treatment strategies, and the magnitude of benefit of well-known therapies in specific risk populations. This chapter outlines recommended adjuvant systemic therapy on the basis of the available evidence of efficacy, as well as in consideration of specific circumstances.

Endocrine therapy

Who should be offered tamoxifen?

Adjuvant tamoxifen 20 mg/day for five years is recommended for all women, both pre-and postmenopausal, with hormone receptor (HR)-positive breast cancer [1,3]. The proportional reduction in 10-year mortality in women of all ages with HR-positive breast cancer treated with 5 years of tamoxifen versus no tamoxifen is 26% [1]. For women with node-negative and node-positive breast cancer, the absolute risk reductions for death with 5 years of tamoxifen are 5.6% and 10.9%, respectively. The 2000 Oxford Overview confirms a significant survival benefit for tamoxifen with 15 years of follow-up, with the most significant proportional improvement starting after 5 years [2].

The risk reductions for death with 5 years of tamoxifen varies depending on the age group assessed. The magnitude of benefit in pre-menopausal women with very low risk node-negative breast cancer, specifically <1 cm, or 1–2 cm with grade 1 histology and no positive lymph nodes, is not known [3]. There is little evidence to support a benefit of CT in this low risk group. In addition, CT-associated short- and long-term sequelae are not negligible, so that women at very low risk of relapse may derive more harm than good from such therapy. By contrast, tamoxifen has a low level of serious side-effects and has been shown to reduce HR-positive contralateral breast cancer [4]. Thus, secondary prevention may be a reason to consider tamoxifen even in women with very low risk HR-positive breast cancer.

In pre-menopausal women with high-risk node-negative or node-positive breast cancer, CT is associated with greater risk reduction for recurrence and death than tamoxifen, however the benefit of each is additive. The difficult issue is to determine how much additional benefit is conferred by adding CT versus the marked increase in treatment-related side-effects with the combined modality treatment. The number of pre-menopausal women treated with adjuvant tamoxifen and with 10 or more years of follow-up is small, and several studies are still exploring the absolute magnitude of tamoxifen benefit in this population (Table 1).

In postmenopausal women, tamoxifen should be offered preferentially if HR are present [1]. Additional benefits of tamoxifen (which are included in the overall estimates of benefit) include a reduction in low density lipoprotein (LDL) and total cholesterol, a probable reduction in the incidence of coronary artery disease-associated deaths, and protection against osteoporosis by stabilising the rate of postmenopausal bone demineralisation [1,5]. The incidence of serious side-effects with tamoxifen is low. There is a 4-fold increase in endometrial cancer over the general population incidence of 0.1% (North America), and a 0.02% risk of endometrial cancer death [1]. The risk of deep venous thrombosis (DVT) and its potential sequelae is in the order

Table 1
Ongoing trials comparing tamoxifen to other hormonal therapies

Trials	Status	*N* target	Results
What is the optimal duration of tamoxifen (Tam)?			
NSABP B-14 (5y vs continued)	Reported	1172	Equivalence for OS; more endometrial cancer with longer
ECOG E4181 E5181 (5y vs continued)	Reported	?	Equivalence for RFS
Scottish (5y vs continued)	Reported	342	Equivalence for RFS, more endometrial cancer with longer
ATTOM (5 vs 10y in ER+ or ER unknown)	Open	?	N/A
ATLAS (5 vs 10y in ER+)	Open	20,000	N/A
What is the optimal 5y hormone therapy: tamoxifen, aromatase inhibitor, or a few years of each?			
BIG 01-98 (L 5y vs Tam 5y vs Tam 2y + L 3y vs L 2y + Tam 3y)	Open	3500	N/A
ATAC (Tam vs Tam + A vs A for 5y)	Maturing	9100	Results expected in early 2002
GABG-IVC (5y Tam vs 2y Tam + 3y A)	Maturing	1300	N/A
BIG 02-97 (Tam 5y vs Tam 2–3y + E 3–2y)	Open	4400	N/A
ABCSG 12 (G + Tam 3y vs G + A 3y)	Open	1250	N/A
Is there added benefit to an aromatase inhibitor after 5y of tamoxifen?			
BIG 01-97/ NCIC MA.17 (L 5y or placebo after Tam 5y)	Open	4800	N/A
ABCSG 06A (A 3y or placebo after Tam 5y)	Open	1700	N/A
NSABP B-33 (placebo or E 2y after Tam 5y)	Open	3000	N/A
What is the optimal timing of tamoxifen in relation to chemotherapy?			
GEICAM 9401 (4EC, sequential vs concurrent Tam 5y)	Open	1000	N/A
INT 100 (Tam vs CAF with concurrent vs sequential Tam)	Closed	1470	Insufficient follow-up for Tam concurrent vs sequential question. 5% absolute survival advantage for CAF + Tam
What is the added value of tamoxifen in ER– disease?			
EORTC 10901 (CT vs CT + Tam 3y)	Open	1816	N/A Note: patients of any ER status are eligible
GABG IVD (3 CMF [1–3 nodes] or 4 EC/3CMF [4–9 nodes] vs same + Tam 5y)	Open	950	Note: patients with hormone receptor-negative status and ≤70 years of age
What is the value of other hormonal therapies in pre-menopausal women?			
EORTC 10901 (CT vs CT + Tam 3y)	Open	1816	N/A
PEAT (1 dose preoperative Faslodex vs placebo)	Open	3500	N/A
NCIC MA12 (Tam 5y vs placebo after chemotherapy)	Open	800	N/A
CRC (Control vs Tam vs LHRHa + Tam vs LHRHa)	Closed	1119	Preliminary results show equivalence
ZIPP (2 × 2 randomisation to Tam vs no Tam and LHRHa vs no LHRHa; any ER status)	Closed	2710	Relative risk 0.76 favouring LHRHa in $n = 860$ randomised to Tam (95% confidence interval 0.61–0.95)
UKCCCR-ABC (Tam vs Tam + CT vs Tam + OA vs Tam + CT +OA)	Open	4000	N/A

Legend: A = anastrozole; ABCSG = Austrian Breast Cancer Study Group; ATAC = ATLAS, Adjuvant tamoxifen longer and shorter; ATTOM = Adjuvant Tamoxifen Treatment Off or More; BIG = Breast International Group; CRC = Cancer Research Campaign; CT = chemotherapy; E = exemestane; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for the Research and Treatment of Cancer; GABG = German Adjuvant Breast Cancer Group; GEICAM = Grupo Español de Investigación en Cáncer de Mama; G = goserelin; INT = Intergroup; L = letrozole; NCIC = National Institute of Canada; NSABP = National Surgical Adjuvant Breast Project; PEAT = Perioperative endocrine adjuvant therapy; Tam = Tamoxifen; ER = oestrogen receptor; OS = overall survival; RFS = relapse-free survival; N/A = not available; y = years; CAF = cyclophosphamide, doxorubicin, 5-fluorouracil; LHRHa = luteinising hormone-releasing hormone; UKCCCR = United Kingdom Co-ordinating Committee on Cancer Research.

of 2%. The benefit risk ratio of tamoxifen must be carefully weighed for patients with a previous history of spontaneous DVT or pulmonary embolism, or with an inherited disorder of coagulation. Of the non-serious, but nevertheless potentially noisome side-effects, including vaginal dryness, depression, cataract formation, and hot flushes, the latter is the most frequent.

Even tumours with very low expression of HRs seem to be sensitive to the effects of tamoxifen [6,7]. However, for women with tumours with no oestrogen (ER) and progesterone receptor (PR) expression, tamoxifen does not significantly reduce relapse or death risk, and is not recommended [1,2]. Whether tamoxifen protects against a second primary cancer in this population is unknown.

Ovarian ablation in pre-menopausal women?

In the absence of CT, ovarian ablation (OA) has been shown to improve survival (absolute improvement 9.8%) and reduce breast cancer recurrence (absolute reduction 8.5%) in women <50 years compared with control [2,8]. Ovarian suppression using a luteinising hormone-releasing hormone analogue (LHRHa) is an alternative to surgical or irradiation-induced castration, with the added advantage of being reversible. The optimal duration of LHRHa suppression, however, is not known: studies using LHRHa have looked at 2, 3, or 5 years, however data is not mature. Whether ovarian ablation is equivalent to adjuvant CT is still unclear. Preliminary results of several comparative trials of LHRHa and cyclophosphamide, methotrexate, 5-fluorouracil (CMF) in pre-menopausal women with node-negative and node-positive breast cancer have been reported. The Zebra trial, comparing 6 CMF (Bonadonna regimen [9]) to goserelin for 2 years in women with node-positive disease shows equivalence in terms of relapse (684 events among 1640 randomised patients, hazard ratio 1.01, $P = 0.94$) and survival (hazard ratio 1.0, $P = 0.92$) for the subset with ER-positive disease, and superiority for CMF in the subset with ER-negative disease (about 19% of the patient population, hazard ratio for disease-free survival (DFS) 1.72, 95% confidence interval (CI) 1.24–2.37) [10]. A Scandinavian trial which randomised 732 women with node-positive disease and/or tumours >5 cm to OA or 9 CMF (i.v. every 3 weeks) has reported no difference in endpoints after 68 months follow-up, with 101 and 103 events in the OA and CMF groups, and 79 and 66 deaths, respectively, (p = NS) [11]. Early results of an Austrian Breast Cancer Study Group trial comparing 6 CMF (Bonadonna regimen) to the combination of OA (goserelin for 3 years) plus tamoxifen (20 mg/day for 5 years) in ER-positive breast cancer patients also showed no difference in overall survival (OS) with a median follow-up of 42 months, despite better relapse-free survival (RFS) ($P < 0.02$) in the OA group (1045 randomised, 157 recurrences, 56 deaths) [12]. Finally, a trial comparing 6 CMF (Bonadonna regimen) to 5 years of tamoxifen (30 mg/day) plus OA showed no difference in DFS or OS with 76 months follow-up [13].

Several randomised trials comparing OA and CT are still accruing or are closed, but unreported (Table 2). Follow-up on reported trials is too short to determine whether overall survival differences will emerge, and all studies conducted thus far have design limitations, including no tamoxifen use and/or suboptimal CT regimens in the 'control' arms. A definitive position on the relative merit of OA compared with CT must be deferred until mature results are available. Consideration of side-effects and adverse sequelae of these therapeutic modalities must also enter the equation when assessing their relative benefits. A part of the benefit of adjuvant CT in pre-menopausal women is derived from the induction of amenorrhea, thus it seems logical that OA also provides some protection against relapse. However, it may be that OA is preferable treatment for some tumours (such as those of low or intermediate grade), but inferior to CT for others (such as those of high grade). This is an area that requires further investigation.

Finally, there is the question of whether the OA provides additional benefit when added to CT and tamoxifen in pre-menopausal women. Preliminary evidence from the most recent Oxford overview found a non-significant decrease in recurrence rate and a non-significant increase in death with the addition of OA to CT [2]. However, ongoing and maturing trials continue to add data to this question, in order to be able to adequately answer it (Table 2). An Intergroup trial has recently reported increased DFS but equivalent OS for women randomised to the combination of cyclophosphamide, doxorubicin, 5-fluorouracil (CAF) CT followed by reversible OA and tamoxifen for 5 years compared with either CAF and OA, or CAF alone, after 6 years median follow-up [14].

Three additional studies, reported in abstract form, fail to show a survival improvement for the addition of OA to CT plus tamoxifen, although in one of these the DFS was superior for the triple therapy, suggesting that follow-up may be inadequate to reliably assess the effect on survival [15–17]. Like

Table 2
Recent trials of chemotherapy (CT) and ovarian ablation (OA) in pre/peri-menopausal women with breast cancer

Trial/group	Status	Population	Arms	Results
GABG-ZEBRA	Closed 12/96	<50 years old NP	OA (Goserelin [G] × 2y) 6 CMF	Preliminary results show equivalence
GABG IVB	Open, accrual target 950		3CMF 4 EC 3 CMF + G 2y 4 EC + G 2y + Tam 5y	Not reported
DBCG	Closed, accrued 732	NP, ER + or T >5 cm	OA 9 CMF	Not reported
IBCSG 11-93	Open, closed for low accrual 174	NP, ER +	OA Tam × 5y OA 4 AC Tam × 5y	Equivalence for 4 year DFS and OS
Intergroup 0101	Closed, reported accrual 1504	NP	CT CT + Zoladex (Z) CT + Z + Tam	RFS, but no OS advantage to Z + Tam + CT arm. Benefit of Z seen in younger women (subset analysis)
FNCLCC	Closed?, target accrual 1000	mandatory CT	OA (surgery, LHRHa, or XRT) No OA	
UKCCCR-ABC	Open, target accrual 4000		Tam Tam + CT Tam + OA Tam + CT + OA	
FASG 06	Closed $n = 333$	HR + 1–3 NP	Tam + Triptoreline x3y 5 $FE_{50}C$	Equivalence for 5 year DFS and OS

Legend: DBCG = Danish Breast Cancer Cooperative Group; ER = oestrogen receptor; FASG = French Adjuvant Study Group; FNCLCC = Fédération Nationale des Centres de Lutte contre le Cancer; GABG = German Adjuvant Breast Cancer Group; HR = hormone receptor; IBCSG = International Breast Cancer Study Group; NP = node-positive; Tam = tamoxifen; UKCCCR = United Kingdom Co-ordinating Committee on Cancer Research; XRT = radiotherapy; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; DFS = disease-free survival; OS = overall survival; LHRHa = luteinising hormone-releasing hormone.

tamoxifen, the magnitude of benefit from OA among pre-menopausal women may vary with age, being more advantageous in younger women. This requires confirmation.

Trials conducted to date have not excluded from participation those pre-menopausal women who develop amenorrhea during CT, a group for which the added benefit of ovarian ablation is probably nil. Thus, the impact of OA on survival in these trials is diluted by this group. The ideal trial design is one in which only women who do not develop CT-induced amneorrhea are randomised to OA versus no OA. Just such a trial is being planned by a large intergroup collaboration.

Predictive factors for hormone responsiveness

Thus far, the presence or absence of HRs appears to be the only reliable predictor of the efficacy of hormonal therapies. Some retrospective data raises the question of whether overexpression of the epidermal growth factor tyrosine kinase receptor, HER2, may be associated with tamoxifen resistance. However, the quality of this evidence leaves us without definite conclusions [18–21]. Women with tumours that overexpress HER2 and have positive HR receptors should not be denied tamoxifen, however, they should be monitored carefully. The relative sensitivity of such tumours to tamoxifen and aromatase inhibitors requires prospective investigation: preliminary results of a neoadjuvant trial (see below) suggest that there may be a difference in sensitivity among HER2-positive tumours.

Ongoing investigations of hormonal therapies

Currently, active randomised controlled trials of adjuvant hormone therapy are examining whether in women with HR + breast cancer, more than 5 years of tamoxifen is superior to 5 years (Table 2). This is based on the observation from the Oxford overviews that the benefit of tamoxifen is greater with 5 years than with 2 or 1 year, and that the benefit of 5 years persists after discontinuation of tamoxifen. Although three randomised studies have thus far reported no benefit for prolonging tamoxifen beyond 5 years,

follow-up may be too early, and the sample size too small in these trials to adequately test the hypothesis [22–24].

At the present time, the use of non-steroidal and steroidal aromatase inhibitors (AIs) in the adjuvant setting must be considered investigational. Preliminary results of a neoadjuvant study have been reported, in which 337 postmenopausal women with HR + breast cancer for which breast conserving surgery was not feasible were randomised to 4 months of letrozole or tamoxifen followed by surgery [25]. Clinical response rates ($P < 0.001$) and breast conservation rates ($P = 0.02$) were significantly better in the group treated with letrozole, pathological response rates were not reported. Whether adjuvant AIs or new selective oestrogen receptor modulators provide similar or superior risk reduction to tamoxifen, with fewer side-effects (particularly a lower risk of thromboembolic disease and endometrial cancer), is being addressed by several randomised trials (Table 1). Whether sequential tamoxifen and AIs enhance survival compared with tamoxifen alone, and whether the combination of OA with tamoxifen or CT or both improves survival, are also being addressed. The value of one preoperative dose of the pure anti-oestrogen Faslodex, which has been shown in vitro to downregulate the HR, is also being addressed prospectively [26]. Preliminary answers to these research questions may be available in the next five years.

Chemotherapy

Recommendations for adjuvant CT are derived from the Oxford overviews of polychemotherapy and the St Gallen consensus on prognostic factors [2,3,27,28]. Three to six months of adjuvant CT with CMF or an anthracycline-based regimen is associated with highly significant 15-year absolute reductions in death for young women (<50 years) with node-negative (7%) and node-positive (11%) breast cancer, and postmenopausal women with node-negative (2%) and node-positive (3%) breast cancer, regardless of the added use of tamoxifen [2,27]. Although not yet published, the Oxford 2000 Overview continues to show a similar magnitude of benefit for these risk groups [2].

When should pre-menopausal women receive chemotherapy?

Pre-menopausal women with node-positive disease and with non-low-risk node-negative disease should be offered adjuvant CT, regardless of their HR status [3,28]. The magnitude of benefit of CT in women with very low-risk node-negative tumours (Table 3) is uncertain, but is probably minimal. The benefit of CT for tumours with no HR expression, but otherwise good prognostic features is unknown, however, most clinicians would recommend CT in this scenario. Recent evidence suggests that women are willing to accept the side-effects of CT for very low absolute gains in survival, a fact that perhaps mitigates in favour of at least discussing the merits and demerits of CT with most pre-menopausal women with breast cancer, no matter how low their risk [29]. The case of very low-risk disease may be one in which CT and OA offer similar benefit, however this requires prospective confirmation. CT should be followed by 5 years of tamoxifen in women with HR+ disease, since their benefits are additive.

The relapse and death rates in women with very high-risk disease, such as >10 positive lymph nodes, locally advanced and inflammatory disease remain unacceptably high, despite (neo) adjuvant CT and endocrine therapy. Whenever possible, women with very high risk of relapse should be offered participation in a randomised clinical trial exploring novel therapeutic strategies. On the other extreme, women with very small tumours that are node-negative and have features suggestive of low aggressive potential, the decision to offer CT must take into consideration the potential for cognitive deficits, secondary leukaemia, and cardiac toxicity associated with some adjuvant regimens [30–32].

When should postmenopausal women receive chemotherapy?

The 1995 Oxford overview reported highly significant 2% and 3% reductions in 10-year death rates after node-negative and node-positive breast cancer, respectively, among women 50–69 years old treated with CT, irrespective of the additional use of tamoxifen [27]. Further follow-up in the Oxford 2000 Overview suggests that the survival advantage seen in the first 4 years of follow-up in this age group seems to endure to the 10 year follow-up mark, and may be attenuated thereafter [2]. The survival advantage appears to be greatest for the subgroup with ER-negative and ER-unknown disease, respectively, while for those with ER-positive disease, the absolute reduction in death was significant following anthracyclines treatment, but less so when the CMF regimen was considered. Further subgroup analyses, such as by number of positive nodes, grade and of trials not confounded by the addition of ineffective therapy (such as tamoxifen plus CT in HR-negative

Table 3
Risk categories for patients with node-negative breast cancer

Characteristic	Minimal/low-risk	Average/high-risk [a]	
		Hormone-responsive [b]	Not hormone-responsive
Hormone receptor status	ER- and/or PgR-positive	ER- and/or PgR-positive	ER− and/or PgR-negative
	must have all characteristics below:	And at least one of the following:	
Pathological tumour size	≤2 cm	>2 cm	Any
Nuclear/histological grade	1	2–3	Any
Age (years)	≥35	<35	Any
Adjuvant therapy recommended	Pre-menopausal: Tam or none Postmenopausal: Tam or none	Pre-menopausal: OA + Tam [±CT] [c] CT + Tam [±OA] [c] Tam or OA Postmenopausal: Tam or CT [d] + Tam	Pre-menopausal: CT [e] Postmenopausal: CT [e]

Adapted from Ref. [28].

[a] Responsiveness to endocrine therapies is related to expression of oestrogen (ER) and progesterone receptors (PR) in the tumour cells. The exact threshold of ER and / or PR staining (with currently available immunohistochemical methods), which should be used to distinguish between endocrine responsive and endocrine non-responsive tumours is unknown. Even a low number of cells stained positive (as low as 1% of tumour cells) identify a cohort of tumours having some responsiveness to endocrine therapies [39]. Probably, as typical for biological systems, a precise threshold does not exist. However empirically chosen, about 10% positive staining of either receptor might be considered as a reasonable threshold, accepted by most. Furthermore, it is clear that the lack of staining for both receptors confers an endocrine non-responsiveness status.

[b] Some Panel members recognise lymphatic and/or vascular invasion as a factor indicating greater risk than minimal or low.

[c] Brackets indicate an addition to the regimen that is being tested in current clinical trials

[d] The addition of chemotherapy is considered an acceptable option based on evidence from clinical trials. Considerations about a low relative risk, age, toxic effects, socioeconomic implications, and information on the patient's preference might justify the use of tamoxifen alone.

[e] For patients with endocrine non-responsive disease, questions of timing, duration, agent, dose, schedules of chemotherapy are subjects for research studies.

CT = chemotherapy; Tam = tamoxifen; OA = ovarian ablation.

disease), are needed to determine the magnitude of benefit of CT in these different risk groups.

CT is the adjuvant treatment of choice for postmenopausal women with HR-negative breast cancer regardless of nodal status, because treatment with tamoxifen is ineffective, and the absolute relapse risk is higher [3]. However, the lower limit of size among HR-negative tumours that benefit from CT is unknown. This may be of particular relevance in older women, since both the tolerance to CT and the absolute benefit (due to competing causes of death) appear to decrease with advancing age.

Node-positive disease is associated with a higher relapse risk than node-negative disease, and the risk increases as the number of involved nodes increases [33]. Thus, for HR-positive disease, the presence of positive axillary nodes, particularly if multiple, merits the consideration of adding adjuvant CT to tamoxifen. Some of the published randomised studies comparing CT plus tamoxifen to tamoxifen alone suggest there is added benefit of CT, while others suggest there is none (Table 4) [34–38]. Many of these trials have similar design flaws as the comparative trials of CT and OA plus CT, however, such as suboptimal CT regimens and less than 5 years of tamoxifen, making their results difficult to interpret. In general, however, it is the studies that examined an anthracycline and that compared 5 years of tamoxifen plus or minus an adequate CT regimen that show a survival advantage for the combination. One such example, was the Intergroup trial (INT 0100) which compared 5 years of tamoxifen to the same given either concurrently with or after completion of 6 cycles of CAF, with a planned total dose intensity of 360 mg/m^2 doxorubicin. With mature follow-up, a highly significant survival benefit has emerged for CAF added to tamoxifen, with a hazard ratio (recurrence) of 1.29 (95% CI 1.04–1.59, $P = 0.001$) and a 5% absolute survival difference (84% vs 79%) [39]. Nevertheless, toxicity was substantial in the CT arm: 4 treatment-related deaths, 41% grade 4 neutropenia, 23% grade 3+ vomiting, 26% grade 3+ stomatitis, 2% congestive heart failure, 6 cases of myelodysplastic syndrome and 3 of acute myeloid leukaemia [39,40].

Whether the magnitude of benefit of CT in HR-positive node-negative breast cancer treated with tamoxifen warrants the associated side-effects is de-

Table 4
Tamoxifen versus chemotherapy plus tamoxifen in postmenopausal women

Trial/group	Status	Treatments	Results
NCIC	Reported, $n = 705$	Tam 2y 6CMF q21d + Tam 2y	Equivalence for DFS, OS at 5 years
ICCG	Reported, $n = 604$	Tam 4y 6 E (60 d1,8 q28d) + Tam 4y)	Equivalence for OS at 5y; DFS 62 vs 74% favouring CT + Tam ($P = 0.02$)
IBCSG	Reported, $n = 1266$	Tam 5y vs CMF early, late, or both + Tam 5y	Equivalence for DFS, OS at 5y
INT 100	Reported, $n = 1477$	Tam 5y CAF + or followed by Tam 5y	5% absolute OS advantage for CT + Tam, $P < 0.05$; $P = 0.001$ for DFS advantage
ABCSG 09	Open, target 660	Tam 5y 4 EC 60/600 q21d + Tam y	N/A
UKCCCR-ABC	Open, target 2000	Tam Tam + CT	N/A
GFEA 07	Open, target 546	Tam 3y 6 FEC (500/50/500 q21d) + T 3y	N/A
GFEA 08	Open, target 534	Tam 3y 8 E 30 d1,8 q21d + T 3y	N/A
Gelber meta-analysis	3920, 9 trials	Tam 1–5y 6–12 CMF or anthracycline + Tam 1–5y	Equivalence for quality-adjusted overall survival 2 individual trials show OS better for CT + Tam: 2y Tam + 24CMF vs 2y Tam 5y Tam + 4AC or 17 PF or 17 PAF vs 5y Tam

Legend: ABCSG = Austrian Breast Cancer Study Group; CT = chemotherapy; E = exemestane; INT = Intergroup; NCIC = National Institute of Canada; Tam = Tamoxifen; OS = overall survival; y = years; CAF = cyclophosphamide, doxorubicin, 5-fluorouracil; UKCCCR = United Kingdom Co-ordinating Committee on Cancer Research; q = every; d = day; FEC = 5-fluorouracil, epirubicin, cyclophosphamide.

batable based on the latest Oxford overview results and the fact that node-negative disease has a better prognosis than node-positive disease.

Given the available evidence, the decision to offer CT to postmenopausal women with HR + breast cancer must be individualised, using clinical judgment and taking into account the number of involved nodes, tumour size and grade, patient age, general health, treatment preferences, and CT-associated toxicity.

The optimal treatment for healthy women older than 69 years is unclear, since most randomised trials have excluded this age group. Elderly women with significant co-morbid illnesses or a short life expectancy who have HR + breast cancer may be best treated with tamoxifen alone, however this requires consideration of individual absolute risk, as it is clear that node-negative disease has a very different risk than disease with 10 positive nodes. CT may be a rational treatment option for fit elderly women with a reasonable life expectancy and HR-negative disease, based on extrapolation of risk and benefit in younger women. The optimal treatment of elderly women with breast cancer represents a wide-open research opportunity, since available evidence is scant.

What is the optimal chemotherapy regimen?

Anthracyclines vs CMF

The choice of CT regimen depends on recurrence risk, co-morbid illness, and patient preference. Anthracycline-based CT is associated with a 4% absolute risk reduction for recurrence and death above that seen with CMF after 10 years follow-up (11% [$2P = 0.0005$] and 16% [$2P < 0.00001$] relative improvements in relapse and death, respectively) [2]. In node-negative disease, the absolute advantage of anthracyclines over CMF is smaller (1.7% at 5 years), given the relatively lower baseline risk [2,27]. A unique toxicity of anthracycline-based CT is the risk of cardiomyopathy. Although the absolute risk is low even with long-term follow-up, it increases with cumulative anthracycline dose and pre-existing cardiac dysfunction and hypertension [32,36]. Both anthracyclines and alkylating agents (cyclophosphamide) are associated with a small risk of secondary leukaemia (Table 5) [31,41].

Anthracycline-based CT should therefore be considered for women with node negative high-risk and node-positive disease, and CMF for women

Table 5
Risks of congestive heart failure (CHF) and acute myeloid leukaemia (AML) after adjuvant chemotherapy

Treatment	Patients with follow-up (*n*)	Median observation period (months)	AML	Rate ($\times 10^{-2}$)	95% confidence interval	% with CHF	% with systolic dysfunction
All epirubicin (E) regimens [a]	3844	34	13	0.009	0.004–0.01	–	–
DI $\leq$ 25 mg/m^2/w	2761	39	5	0.004	0.001–0.01	–	–
DI > 25 mg/m^2/w	1083	28	8	0.02	0.01–0.05	–	–
All non-E-based regimens	1494	36	1	0.001	0.0001–0.009	–	–
Doxorubicin regimens [b]	200	132	–	–	–	1.5	8
CMF regimens [b]	155	132	–	–	–	0	2

[a] From: Pharmacia Clinical Trials Database.
[b] Median age at randomisation into trial was 47 years and at recall for cardiac evaluation was 58 years. From Ref. [32].
CMF = cyclophosphamide, methotraxate, 5-fluorouracil.

with either low-to-moderate relapse risk or high risk of cardiac toxicity (elderly, pre-existing hypertension, pre-existing cardiac dysfunction). Anthracyclines are generally preferred for pre-menopausal women, given that young age is an independent negative prognostic factor [3]. In postmenopausal women for whom CT is warranted, the benefit harm ratio should be carefully considered when choosing the CT regimen.

Taxanes vs no Taxanes

The value of adding taxanes to standard adjuvant regimens is still speculative. There are few ongoing large trials exploring their benefit exclusively in node-negative disease. Trials involving more than 24,000 women are addressing their role in node-positive early breast cancer, however only a few have been reported to date (Table 6). The Cancer and Leukemia Group B (CALGB) 9344 trial of 4AC followed or not by 4 cycles of paclitaxel (T 175 mg/m^2 every 3 weeks) showed a significant 2% ($P < 0.05$) survival advantage for the taxane arm at 21 months follow-up, however that advantage appears to be diminishing with longer follow-up [42–44]. The confounding factor of 12 weeks longer therapy in the taxane arm makes it difficult to determine what, if any, benefit derives from the non-cross resistant taxane. A smaller MD Anderson trial, of 8 cycles of FAC compared with 4 cycles of paclitaxel (T 225 mg/m^2 every 3 weeks) followed by 4 cycles of FAC,

Table 6
Adjuvant taxane trials

Trial	Status	Sample size	Results
Paclitaxel			
CALGB 9344 [a]	Reported	3170	2% OS advantage for AC/T $P = 0.074$; ($P = 0.053$ Wilcoxon)
MD Anderson [a]	Reported	5242	4% relative risk reduction death for T/FAC (P = NS)
NSABP B28 [a,b]	Maturing	3066	Equivalence for OS $P = 0.98$ and DFS $P = 0.38$ at 34 m f/u
ECTO	Open	1250	N/A
MIG-5	Open	1000	N/A
MA.21	Open	1500	N/A
Docetaxel			
NSABP B-27[1]	Closed	3000	N/A
ECOG[1]	Closed	2500	N/A
FNCLCC[1]	Closed	2000	N/A
TAX316[1]	Closed	1200	N/A
BIG 2-98	Closed	2800	N/A
ANGLO CELTIC II	Open	750	N/A
GEICAM 9805	Open	1054	N/A
ICCG C/14-96	Open	800	N/A

Legend: ANGLO CELTIC = Anglo Celtic Group; CALGB = Cancer and Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; ECTO = European Cooperative Trial in Operable Breast Cancer; FNCLCC = Fédération Nationale des Centres de Lutte contre le cancer; f/u=follow-up; GEICAM = Grupo Espanol de Investigacion en Cancer de Mama; ICCG = International Collaborative Cancer Group; m = months; MIG-5 = Gruppo Oncologico Nord Ovest) — Mammella Intergruppo; NSABP = National Surgical Adjuvant Project for Breast and Bowel Cancers; BIG = Breast International Group; T = paclitaxel.

shows a non-significant 24% reduction in relapse for the taxane arm, and the large NSABP B-28 trial ($n = 3066$) of similar design to the CALGB trial (4AC followed or not by T 225 mg/m^2 every 3 weeks × 4 cycles) shows no difference in survival or relapse for the two arms after about 30 months follow-up [45,46]. No trials exploring the added value of docetaxel have been reported yet. Unique toxicities of taxanes include peripheral sensory neuropathy, myalgias and arthralgias, allergic hypersensitivity (paclitaxel), fluid retention syndrome (docetaxel), and rarely, toxic typhlitis [43,47].

Results of the ongoing trials are needed to clearly understand the role of adjuvant taxanes [48]. In particular, the overall evidence may help us identify whether paclitaxel and docetaxel have similar efficacy, and whether there are particular patient groups that derive significant benefit from the addition of taxanes, such as women with HR-negative tumours, as suggested by a subgroup analysis of the CALGB 9344 trial [43]. The CALGB regimen has been approved in the United States for adjuvant therapy in women with node-positive breast cancer, however confirmatory evidence of benefit is of critical importance, particularly when adjuvant regimens of longer duration and potentially more toxicity are being considered for routine use.

What is the optimal dose, schedule, and duration of adjuvant CT?

CMF

The classic Bonadonna CMF regimen, consisting of cyclophosphamide (C) 100 mg/m^2 orally days 1–14, methotrexate (M) 40 mg/m^2 days 1 and 8 intravenously (i.v.), and 5-fluorouracil (F) 600 mg/m^2 days 1 and 8 i.v. every 28 days, is the mostly widely tested CMF schedule. However, variations, such as giving all drugs once every 3 weeks i.v., or C i.v. days 1 and 8, are also in common use [9,49]. Bonadonna showed retrospectively that dose intensity was important, survival being better in women who received at least 85% of the planned doses of CMF [50]. In addition, prospective studies in the metastatic setting have demonstrated inferior survival for the once-every-3-weeks schedule compared to the Bonadonna regimen [51,52]. Although these regimens have never been formally compared in the adjuvant setting, these observations raise the concern that modifications to the Bonadonna regimen may reduce the efficacy of CMF, perhaps because the chief benefit of C is in chronic continuous rather than bolus dosing. It is probably prudent to give the classic CMF regimen preferentially, reserving the i.v. C days 1 and 8 variation for women who are unable to tolerate oral C due to nausea, or who are unwilling to consider losing their hair.

One prospective study has demonstrated that 6 cycles of CMF are as effective as 12 [53]. Trials comparing only 3 cycles of CMF to 6 or 9 have insufficient follow-up to determine if fewer than 6 cycles is equally effective or if there are any subsets for which this is an adequate regimen. At least one (International Breast Cancer Study Group IV), however, reported superiority for 6 versus 3 cycles of CMF, particularly for women who were young or women with HR-negative tumours [54]. The majority of clinicians would advocate cycles of CMF to achieve maximum benefit.

Anthracyclines

There are many anthracycline-containing adjuvant CT regimens in use worldwide for breast cancer. Doxorubicin (A) or epirubicin (E) and C, (AC or EC) are commonly used regimens, sometimes followed by several cycles of CMF in Europe. There are innumerable variations on the number of cycles, length of cycle, and dose per cycle of the drugs in the adjuvant combination F, E or A, and C (FEC/CEF, FAC/CAF), and the choice of schedule and number of cycles appears to depend on clinician and centre experience. However, several points should be borne in mind when selecting an anthracycline-containing regimen.

Duration of anthracycline-based chemotherapy

Four cycles of AC or EC may be inferior to anthracycline regimens that are longer. This is based on the observation that studies that have compared 4 cycles of anthracycline-containing combinations to CMF have shown equivalence, such as the National Surgical Adjuvant Breast Project (NSABP) B-15 trial comparing 4AC to 6CMF (classic regimen) [55]. By contrast, studies that have compared more than 4 cycles of anthracycline regimens such as CAF, and Canadian CEF to CMF have shown superiority for the anthracyclines [56–58]. Other factors which may have influenced the difference in treatment effect, whose impact cannot be determined, are the addition of 5-fluorouracil, oral versus i.v. cyclophosphamide (in CMF), and the day 1 + 8 every 28 day versus day 1 every 21 day schedules (both regimens). Finally, a few studies that directly compared anthracycline-containing combinations that differed only in the dose per cycle of anthracycline or total number of cycles found that more cycles of anthracyclines were better than fewer [59,60]. There appear to be two distinct risk profiles for breast cancer, with associ-

Table 7
Adjuvant trials of Herceptin in HER2-overexpressing breast cancer

Group/trial	Target accrual	Design	Tamoxifen ×5 years	HER2 eligibility
NCCTG N9831	3000	4 AC then T/weekly/x12 4 AC then T/weekly/x12 then H x12 m 4 AC then T + H/weekly/x12 then H x12 m	All ER (+) patients	3 + by IHC or FISH amplified with 2+
BCIRG	2400	AC then 4D AC then 4D then H x12 m 6D + carbo/CDDP with concurrent H x12 m	All ER (+) patients	FISH amplified
NSABP B31	2700	4 AC then 4T 4 AC then 4T + H/weekly then H x12 m	All patients except ER/PgR (−)	3+ by IHC or FISH amplified with 2+
BIG (HERA trial)	3200	Any chemotherapy then H q3weeks x12 m Any chemotherapy then H q3weeks x24 m Any chemotherapy then no H	Not mandatory; each centre to set a policy a priori	3+ by IHC or FISH amplified

Legend: CDDP = cisplatin; IHC = immunohistochemistry; FISH = fluorescent *in situ* hybridisation.

ated recurrence incidences peaking at either two or five years from diagnosis [61]. It is hypothesised that the duration (number of cycles) may be of particular relevance for cancers that have a high risk of early recurrence, such as tumours that are HR-negative or HER2-positive. An additional reason for reduced efficacy of shorter versus longer anthracycline regimens may be a lower rate of CT induced-amenorrhea with the former. Thus, 4AC/EC may not be the optimal anthracycline regimen for women with high-risk disease, but may be reasonable in women with moderate relapse risk.

Dose intensity of anthracycline-based regimens

Although dose intensification of anthracyclines and cyclophosphamide have failed to show superiority over the doses in AC 60/600 mg/m^2 or epirubicin 75–100 mg/m^2, suboptimal dose-intensity and/or cumulative doses are clearly linked with inferior survival [49,59,62–65]. Thus, a concerted effort must be made to deliver CT on time and at the planned doses, using colony growth stimulating factors and/or prophylactic antibiotics after an episode of prolonged or febrile neutropenia that interferes with delivery of subsequent cycles. High dose CT with stem cell transplant after induction CT has not been shown to enhance survival or significantly reduce recurrence in multiple node-positive breast cancer, and should only be offered as part of a randomised clinical trial [66–69]. Three additional trials, reported in the proceedings of the 2001 American Society of Clinical Oncology annual meeting also fail to show a survival advantage for high dose therapy [70–72].

Predictive factors for chemotherapy

Certain tumour characteristics may independently predict for sensitivity to a particular CT drug class. HER2 overexpression is associated with more aggressive disease, earlier relapse, and poorer prognosis than tumours that do not overexpress HER2 [73]. Overexpression of HER2, particularly at the 3+ level by immunohistochemistry, has been shown to predict for response to anti-HER2 therapy in metastatic disease [74]. Adjuvant trials are currently exploring the added value of adjuvant Herceptin, an anti-HER2 antibody, to CT and tamoxifen in women with tumours that overexpress HER2 (Table 7). Women with such tumours should be encouraged to participate in Herceptin trials. HER2 overexpression may also predict for relative sensitivity to anthracyclines and anthracycline dose intensity, however evidence supporting this is retrospective and not rigorous enough to allow us to draw firm conclusions [75–80].

Mutations of *TP53*, which when functioning normally initiates apoptosis or cell cycle arrest and repair in response to DNA damage in cycling cells, predict for relative sensitivity to taxanes and resistance to anthracyclines in laboratory models [81,82]. The EORTC-BIG 01-00 trial is examining this hypothesis prospectively in patients with large operable and locally advanced breast cancer.

Other predictive factors for CT efficacy remain elusive. However, evolving expertise with molecular biology and DNA microarray analysis holds promise of identifying new genes or patterns of gene expression that can reliably individualise the optimal CT regimen.

Conclusions

Pending mature results of ongoing randomised trials comparing 5 years to >5 years of tamoxifen and of newer hormonal therapies, 5 years of tamoxifen remains the recommended standard hormonal therapy for all women with HR-positive breast cancer, regardless of age and other adjuvant therapy received, unless there is high risk of DVT, pulmonary embolism, or endometrial cancer. In pre-menopausal women, CT is preferable to OA based on a larger body of evidence supporting the benefit of the former, but OA is reasonable in selected women with HR-positive tumours of low aggressive potential. Maturing trials comparing OA plus tamoxifen to CT plus tamoxifen may identify an optimal disease and patient profile for each therapeutic modality. Adequate dose intensity and total dose anthracyclines are preferred over CMF in women who are young, have high-risk disease, and who have no risk factors for congestive heart failure. CMF remains an effective alternative in low-risk disease that merits CT and for women at risk of heart failure. The added value of taxanes is currently under investigation. Confirmation of the predictive value of HER2 overexpression and *TP53* mutation in predicting response to specific cytotoxic drugs, and the identification of additional putative predictive factors, is of high priority. Better risk stratification and treatment individualisation are the goals of such research, with improved overall cure rates being the anticipated consequence.

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