Eur J Cancer Clin Oncol, Vol. 19, No. 12, pp. 1753–1770, 1983.
Printed in Great Britain.

0277-5379/83$3.00+0.00
Pergamon Press Ltd.

Adjuvant Systemic Therapy in Breast Cancer; a Review

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PART 1. CHEMOTHERAPY RATIONALE

PRIMARY breast cancer is now generally viewed as a systemic disease. It was previously thought that the primary tumor spreads locally by direct extension and by lymphatics to the regional lymph nodes, and it was believed that the cancer was disseminated by the blood stream to distant sites only at the latest stages of the disease. This traditional concept stimulated aggressive loco-regional treatments, but survival rates have remained unchanged for decades.

The concept of primary breast cancer as being a systemic disease is substantiated by the fact that 70–80% of patients die of disseminated disease [1, 2]. Also, experimental models indicate that once the primary tumor is diagnosed, the tumor has already been through 30 of its 40 doublings, the number that is lethal to the patient [3]; also, it has recently been demonstrated that about half of the patients with clinically localized disease harbor micrometastases [4].

Systemic therapy with drugs of proven efficacy in advanced breast cancer, given as an adjuvant to the primary local therapy, is therefore rational and theoretically represents the best chance of improving the prognosis of primary breast cancer.

Mendelsohn [5], and subsequently Skipper [6], have defined the concept of a growth fraction in tumor cell populations. In micrometastases, as opposed to large tumor masses, the kinetics of growth approach an exponential fashion, i.e. with constant growth fractions and tumor doubling times, and the cell kill to cytotoxic agents follows a first-order kinetics [6]. Accordingly, a drug may kill 99.9% of cancer cells, no matter how many there are. Thus, in a micrometastasis of 100 cells, there is a high statistical probability that all would be destroyed by a given dose of chemotherapy, and that the host would be cured. However, in a metastasis consisting of 10^{10} cells, the same chemotherapy would leave 10^6 viable cells with a potential of regrowth. This principle indicates that the optimal time for chemotherapy to eradicate all cells is immediately after tumor reductive surgery, when the number of residual cells is smallest.

In agreement with these observations, a large number of experimental studies of adjuvant cytotoxic therapy have shown that the smaller the number of residual tumor cells, the greater the chemotherapeutic cure rate [7]. In these studies it has also been demonstrated that multiple drug chemotherapy is superior to single-agent therapy. Because the doubling times of breast cancers range from 20 to 200 days [8], one would expect that, to be effective, adjuvant chemotherapy should be sustained for long periods of time.

TREATMENT RESULTS

Recurrence-free survival (RFS)

The results of early studies have recently been reviewed [9]. The results of some of these trials suggested a benefit from adjuvant chemotherapy to premenopausal patients with 3 or more positive axillary nodes. However, the study design may be considered inappropriate mainly because the rationale was based on the assumption that treatment failure was due primarily to dislodgement of cancer cells during mastectomy. Furthermore, cytotoxic agents were thought to be active as zero-order kinetics, and adequate selection of patients according to prognostic factors was lacking. For these reasons the studies included the administration of short-term postoperative chemotherapy to a patient population often heterogeneous as far as primary local treatment and risk factors were concerned.

One of these early trials, conducted by the Scandinavian Adjuvant Chemotherapy Group, warrants further consideration. This randomized

trial was started in 1965 with the participation of 12 institutions in Norway, Sweden and Finland [10]. Patients ≤70 yr of age with operable breast cancer (T_1–T_3, N_0–N_2, M_0) were included in the study. Primary treatment was radical or modified radical mastectomy for 80% of the patients and simple mastectomy for the other 20%. Assessment of nodal status was done clinically and/or histologically. Postoperative radiotherapy was given to 98% of the patients. In addition, oophorectomy or ovarian irradiation was used routinely in 26% of the patients with poor prognosis, but the criteria were not defined. However, these patients were equally distributed in the two treatment groups.

Patients were randomized perioperatively to either no further treatment or treatment with cyclophosphamide 30 mg/kg body wt (max. 2400 mg) i.v. over a 5-day period.

One thousand, one hundred and eighty-eight patients were randomized, of which 1136 were evaluable: 559 in the treatment group and 577 controls; 1026 were randomized to receive systemic therapy a few hours after mastectomy, but in 110 cases chemotherapy was delayed for about 6 weeks after operation to enable completion of radiotherapy. At 4 yr there was a significant difference both with regard to RFS and survival, but no differences were observed in 110 patients with delayed chemotherapy. These results were reaffirmed after 14 yr of follow-up [11].

In the early '70s two large adjuvant studies were initiated, both including a non-treated control group [12, 13].

The NSABP study was initiated in September 1972 [12]. Patients having radical or modified radical mastectomy for potentially curable breast cancer and having histologically positive axillary nodes entered the study (protocol 05) from September 1972 to May 1975, of which 348 were found to be eligible. Patients were stratified according to institution, age (≤49, ≥50) and axillary nodal status (1–3, >4) and randomized to receive either placebo ($n = 169$) or L-phenylalanine mustard (L-PAM) ($n = 179$) 0.15 mg/kg daily for 5 days, repeated every 6 weeks for 2 yr. The preliminary results, based on a total of 125 patients, were published in 1975 [12]. With an average follow-up period of only 8–9 months, the RFS was 22% in the placebo group compared to 9.7% in the L-PAM group. In a subsequent report [14] it was demonstrated that the initial results in the placebo group were identical with the results from a previous mastectomy trial (protocol 04, $n = 335$), and similarly, that the results from the L-PAM patients in protocol 05 were identical with the results from the same treatment ($n = 346$) in the subsequent protocol comparing L-PAM with L-PAM + 5-fluorouracil (5-FU). Therefore in the following analysis the L-PAM patients in the two studies are pooled (179 + 346 = 525), as are the controls (169 + 335 = 504). After 5 yr the RFS in the L-PAM-treated patients is significantly higher than in the controls [15]. However, it is apparent that this benefit is due almost exclusively to the difference which appeared during the first year of therapy.

The Milan study started in June 1973 [13]. The entry criteria were identical with those of the NSABP study. Patients were stratified by age (≤49, 50–75) and nodal status (1–3, ≥4) and randomized to receive no further therapy or 12 cycles of cyclophosphamide, methotrexate and 5-FU (CMF), starting 2–4 weeks after surgery. From June 1973 to September 1975 a total of 391 patients were randomized, of which 386 were considered evaluable (207 CMF, 179 controls). The results of this trial have been published repeatedly during the last 5–6 yr, with minor inconsistencies in the reported overall recurrence rates, which, nevertheless, do not alter the conclusion from publication to publication. After 6 yr [16] the difference in favor of the CMF group is still significant. It is also apparent that the benefit occurs mainly within the first 3 yr after mastectomy.

Since the first publication of these two studies in 1975 [12] and 1976 [13] numerous surgical adjuvant studies have been initiated. The majority of these are non-randomized, using simultaneous or historical control groups, which renders valid conclusions as to the benefit of adjuvant therapy impossible. However, some randomized studies including a control group but still with limited time of observation have been published during recent years. Among these, the results from two major studies of adjuvant CMF [17, 18] and one of L-PAM [19] with 3–4 yr of follow-up (Table 1) have confirmed the benefit of CMF [17, 18] but not of L-PAM [19]. The two CMF studies included 491 patients [18] and 114 patients [17] respectively randomized to no therapy or 12-monthly cycles of CMF, and in the L-PAM study [19] 364 patients were randomized to no adjuvant therapy vs 2 yr intermittent L-PAM. The ultimate role of L-PAM as an adjuvant thus remains questionable.

Other published randomized studies of adjuvant chemotherapy given to node-positive patients controlled with a no-treatment group and with a minimum median time of observation of 2 yr have also given inconsistent results. In a study from Denmark [18] oral cyclophosphamide given intermittently to premenopausal patients significantly decreased the recurrence rate. In a study from Japan [20] a combination of mitomycin C

Table 1. Adjuvant chemotherapy; randomized trials including a non-treated control group

Reference	Menopausal status/age group	Treatment	Duration	No. of patients treated	Follow-up time (yr)	Overall benefit of CT (*P* value)
[21]	Pre + Post <70 yr	CVF	day 1, q. 4 weeks × 6	97	2	yes (<0.001)
		CVM	day 6, q. 4 weeks × 6			
[22]	Pre + Post	L-PAM	days 1–5, q. 6 weeks × 16	~135	2	no
		M	day 1, q. 6 weeks × 16			
[20]	Pre + Post ≤70 yr	MM-C	days 0, 3, 5	59	2–16	N_{1-3} yes (<0.05)
		C	daily 9+/ 6 months			$N_{\geq 4}$ no
[24]	Pre + Post	LMF + BCG	q. 4 weeks × 6	59	4	no
[17]	Pre + Post ≤70 yr	CMF	q. 4 weeks × 12	64	4	yes (0.001)
[18]	Pre	CMF	q. 4 weeks × 12	306	1–5	yes (0.0001)
[18]	Pre	C	days 1–14 q. 4 weeks × 12	314	1–5	yes (0.0009)
[19]	Pre + Post ≤70 yr	L-PAM	days 1–5 q. 6 weeks × 16	187	3–7	no (0.11)

Abbreviations: Pre = premenopausal; Post = postmenopausal; C = cyclophosphamide; V = vincristine; M = methotrexate; F = 5-fluorouracil; L = chlorambucil; MM-C = mitomycin-C; BCG = Baccille Calmette-Guenrin; L-PAM = melphalan (L-phenylalanine mustard).

(MM-C) and oral cyclophosphamide significantly reduced the recurrence rate in patients with 1–3 positive nodes ($P < 0.5$) but not so if ≥4 positive nodes were found, and a study by the Multicentre Breast Cancer Chemotherapy Group [21] demonstrated a significant benefit of a 6-month adjuvant treatment with a CVF/CVM combination. However, no benefit was described in three studies [22–24] using 3-weekly VACM [23], an intermittent oral combination of L-PAM + MTX (methotrexate) continued for 2 yr [22] and a 6-month treatment with LMF [24] respectively. However, it should be emphasized that in two of these trials [22, 24] rather low doses of chemotherapy were administered.

Survival

In most studies the median time of follow-up is still limited to a few years. However, two studies [11, 16], both of which indicate an improved RFS in the treated group as compared to a control group, have also demonstrated an increased survival at 6 [16] and 15 yr [11] respectively. In the first study the 6-yr survival rate was 73.9% in the CMF-treated group compared to 64.5% in the control group ($P = 0.12$), but this difference was significant only in the premenopausal patients ($P = 0.002$) and not in postmenopausal patients ($P = 0.57$). In the other study [11] the 15-yr survival rate was 52% in the cyclophosphamide treated group compared to 37% in the control group ($P < 0.05$).

Although the available data from randomized adjuvant chemotherapy trials including a non-treated control group are somewhat conflicting, the overall benefit of adjuvant chemotherapy regarding RFS is evident. In the following sections the benefit will be further analysed in relation to different prognostic factors. In addition, the efficacy of adjuvant chemotherapy will be evaluated in relation to the number of cytotoxic drugs used, duration of therapy, dose level and drug-induced toxicity.

EFFICACY OF ADJUVANT CHEMOTHERAPY IN RELATION TO PROGNOSTIC FACTORS

Adjuvant cytotoxic therapy is often harmful to the patient and the socio-economic implications of this therapy are considerable. Therefore it is of the utmost importance to be able to identify subgroups of patients who definitively benefit from the treatment and also subgroups who may possibly be overtreated. A number of trials provide data on the relation between RFS and a number of prognostic factors as evaluated retrospectively. These will be briefly summarized.

Number of positive lymph nodes

A number of trials have analyzed the efficacy of adjuvant therapy in relation to the number of involved axillary nodes [15–20]. As shown in Table 2, the available data are conflicting.

Only three trials have been published dealing with adjuvant chemotherapy to node-negative

Table 2. Benefit of adjuvant chemotherapy (P values) in relation to number of positive lymph nodes: results from randomized trials with a non-treated control group

Reference	Menopausal status	Treatment	Follow-up time (yr)	No. of positive nodes 1-3 (P)	⩾4 (P)
[20]	Pre + Post	MMC + C	2-16	yes (<0.05)	no
[15]	Pre	L-PAM	2	yes (0.02)	yes (0.0006)
	Post	L-PAM	2	no (0.8)	no (0.1)
[16]	Pre	CMF	6	yes (0.001)	yes (0.005)
	Post	CMF	6	no (0.10)	no (0.18)
	Pre + Post	CMF	6	yes (<0.001)	no (0.27)
[17]	Pre + Post	CMF	5	no (>0.05)	yes (0.003)
[19]	Pre	L-PAM	3-7	no (0.08)	no (0.33)
	Pre + Post	L-PAM	3-7	no (0.26)	
[18]	Pre	C	3	yes (0.0003)	no (0.25)
[18]	Pre	CMF	3	yes (0.001)	yes (0.03)

Table 3. Benefit of adjuvant chemotherapy (CT) in node-negative tumors; results from randomized trials with a non-treated control group

Reference	Menopausal status/ age group	Treatment	No. of patients treated	Follow-up time (yr)	Effect in favor of CT (P value)	Effect in node-positive patients
[20]	Pre + Post ⩽70 yr	MMC + C	102	2-16	no (>0.05)	yes
[23]	Pre + Post <65 yr	LMF	177	2	no (0.50)	no
[24]	Pre + Post	LMF + BCG	58	4	yes (0.003)	no

patients [20, 23, 24]. As shown in Table 3, two of the studies failed to demonstrate any benefit, and in one of these [20] a benefit was also observed with the same treatment in node-positive patients. Conversely, the study from Switzerland [24] observed a benefit in node-negative but not in node-positive patients.

The node-negative patients probably represent those with the least residual tumor cells after primary local treatment and would thus represent patients with the greatest chance of cure with adjuvant systemic therapy. However, the recurrence rate in these patients is relatively low (25-40%) and therefore improved methods of recurrence prediction are needed to select subgroups for adjuvant systemic therapy.

Menopausal status

The randomized trials with a non-treated control group presenting data relevant to menopausal status are in Table 4. In the early trials of NSABP [15] and from Milan [16] the RFS was significantly increased only in the premenopausal patients. Whether these findings may be related to inadequate doses given to the postmenopausal patients will be discussed later.

As shown in the table, the results of three trials reveal no effect in both pre- and postmenopausal patients [19, 23, 24], whereas two other trials [11, 17] demonstrate a beneficial effect in postmenopausal patients. It should also be noted that in a preliminary report of a study with CMF by Rubens [17] no benefit was observed in the premenopausal patients.

Another four randomized trials that have been published are presented in Table 5. Three of these compared single-drug therapy with multiple-drug therapy [15, 25, 26]. All demonstrate differences in favor of the multiple-drug combinations, and in two of these [15, 26] this benefit is also present among the postmenopausal patients.

In conclusion, the available data indicate that adjuvant chemotherapy may be effective in both pre- and postmenopausal patients.

Oestrogen receptor (ER) status

To date only limited data analyzing ER status have been published [16, 23, 28]. Data from the Milan study of 6 or 12 cycles of CMF [28] have shown the 3-yr RFS in premenopausal ER-positive and -negative tumors to be 82.9 and 72.8%

Table 4. Benefit of adjuvant chemotherapy (P values) in relation to menopausal status; results from randomized trials with a non-treated control group

Reference	Treatment	Follow-up time (yr)	Benefit (*P* value) Pre	Post	Pre + Post
[15]	L-PAM	2	yes (<0.001)	no (0.09)	yes (0.004)
[23]	VACM	2	no (0.21)	no (0.26)	no (0.13)
[24]	LMF + BCG	4	no (0.80)	no (0.49)	no (0.40)
[17]	CMF	5	no (>0.05)	yes (0.003)	yes (0.001)
[11]	C	15	yes (<0.05)	yes (<0.05)	yes (<0.001)
[16]	CMF	6	yes (<0.001)	no (0.35)	yes (0.001)
[19]	L-PAM	3–7	no (0.14)	no (0.39)	no (0.11)

A = Adriamycin.

Table 5. Adjuvant chemotherapy: Benefit (P values) in relation to menopausal status; results from randomized trials

Reference	Treatments	Follow-up time (yr)	Benefit (*P* value) Pre	Post	Pre + Post
[25]	CMF vs L-PAM	2	yes (<0.05)	no (>0.8)	
[15]	L-PAM + F vs L-PAM	2	yes (<0.04)	yes (0.002)	yes (<0.001)
[26]	CMFPV vs L-PAM	4½	no (>0.05)	yes (0.008)	yes (0.005)
[27]	CMFVP vs CMF	2	yes (0.05)	no (0.11)	yes (0.01)

respectively ($P = 0.23$). The corresponding figures in the postmenopausal patients were 81.9 and 75.2% respectively ($P = 0.82$). Similar relationships have been observed at 4 yr [16]. It should be stressed that these figures only indicate an identical prognosis in ER-positive and -negative tumors treated with CMF but do not actually analyze the efficacy in relation to chemotherapy. However, no data of the RFS in the CMF-treated group compared to the control group and in relation to ER status are presented. Another study from the U.K. [23] presenting these relationships also failed to demonstrate any significant relation between ER status and effect of adjuvant chemotherapy. Further analyses should be made in this field.

In conclusion, the available data fail to demonstrate significantly any subgroups which benefit any more than the total treatment groups. This may be due to several reasons: different patient selection criteria, different operations with varying numbers of lymph nodes available for examination, different application of adjuvant radiotherapy, different chemotherapies and different times of observation.

As far as the latter problem is concerned, one would expect the relationship between a therapeutic benefit and a prognostic variable to change with time, and Table 6 illustrates that this might well be the case. This table gives the *P* values for the benefit of 12 cycles of CMF over the control group in relation to the number of involved nodes and the time of observation. As can be seen, the *P* value is constantly 0.001 or less for 1–3 nodes but for the worse prognostic factor, ⩾4, the *P* value gradually decreases from highly significant to non-significant values. This also emphasizes the need to specify the statistical tests used, as some tests (Gehan) give special weight to the initial phase while others (log rank) specifically weigh the later phase of the curves.

Future trials should re-analyze the efficacy of adjuvant chemotherapy in relation to known prognostic factors and should also include analyses of the importance of a number of histological and biochemical properties of the primary tumor with the aim of developing improved methods of prediction of the efficacy of adjuvant chemotherapy.

SINGLE- VS MULTIPLE-DRUG CHEMOTHERAPY

Three studies (Table 7) compare single- and multiple-drug therapy in relation to a control

Table 6. Benefit of adjuvant CMF compared to a control group in relation to number of positive nodes and time of observation

Reference	Follow-up time (months)	No. of positive nodes (*P* value) 1–3	⩾4
[13]	26	0.0001	0.00001
[29]	36	<0.001	0.005
[30]	48	0.0007	0.03
[44]	72	<0.001	0.27

Table 7. Adjuvant chemotherapy: single vs multiple-drug trials including a control group

Reference	Trial	No. of patients	Follow-up time (yr)	Comparisons	*P* value
[15]	control	505		control vs L-PAM	0.004
	L-PAM, 2 yr	525	3–5	control vs L-PAM + F	<0.001
	L-PAM + F, 2 yr	689		L-PAM vs L-PAM + F	0.02
[17]	control	261		control vs L-PAM	>0.05
	L-PAM, 2 yr	186	5	control vs CMF	0.001
	CMF, 1 yr	135		L-PAM vs CMF	0.2
[18]	control	185		control vs C	0.0009
	C, 1 yr	314	3	control vs CMF	0.0001
	CMF, 1 yr	306		C vs CMF	0.34

group. As mentioned previously, the NSABP study [15] actually consisted of three consecutive studies with later pooling of the results from identical treatment groups. As shown in the table, a difference in favor of the multiple-drug combination is as yet demonstrable only in the NSABP study, whereas in the two other studies L-PAM [17] as well as C [18] do not differ from CMF. It should be stressed, however, that in the study by Rubens [17] CMF, as opposed to L-PAM, was significantly superior to the control.

Six other studies have compared single-drug therapy, in all cases L-PAM, with multiple drug therapy. As shown in Table 8, all but one study [33] reported the combinations to be superior to L-PAM.

Another two major studies compared CMF with AVCF [35] and CMFVP [27] respectively. In the first study the treatments were given for 1 yr and in the other for 2 yr; however, during the second year VP was omitted from the CMFVP combination. In both studies, now with up to 3 yr and a median of 2 yr of observation respectively, CMF is significantly inferior to the 4–5-drug combinations ($P = 0.0015$ and 0.01 respectively). The majority of data thus indicate that combinations are superior to single-drug treatments.

Table 8. Adjuvant chemotherapy: single- vs multiple-drug trials

Reference	Trial	No. of patients	Follow-up time (yr)	Benefit of combination compared to L-PAM (*P* value)
[25]	L-PAM, 1 yr	51	2	yes (N.I.)
	CFP, 1 yr	58		
[31]	L-PAM, 1 yr CFP, 1 yr CFP + BCG, 1 yr	194	2 (mean)	yes (0.0495)
[32]	L-PAM, 2 yr	42	4	yes (0.05)
	CMF, 2 yr	44		
[26]	L-PAM, 1 yr	254	4½	yes (0.005)
	CMFV, 1 yr			
[33]	L-PAM, 2 yr	94	3	no (0.3)
	CMF, 2 yr	77		
[34]	L-PAM, 2 yr	167	4 (mean)	yes (0.002)
	CMFVP, 1 yr	145		

N.I. = not indicated.

Table 9. Duration of adjuvant chemotherapy

Reference	Treatment	*n*	Follow-up time (yr)	Result
[16]	CMF × 6 vs CMF × 12	325	4	N.D.
[36]	CMF × 6 vs CMF × 12	143	2 (mean)	N.D.
[37]	AC × 5 vs AC × 10	200	2½ (mean)	N.D.
[38]	CMF × 1 vs CMF × 12	954	1	12 superior to 1
[40]	LMF × 6 vs LMF × 24	386	3	N.D.
[41]	CMFVP 1 yr vs CMFVP 2 yr			T.E.

N.D. = no difference. T.E. = too early.

TIME TO START AND THE DURATION OF THE ADJUVANT THERAPY

In the vast majority of studies the adjuvant therapy was started 0–4 weeks after operation and no randomized studies analyzing the optimal time to start the therapy have been published. Retrospectively, Nissen-Meyer *et al.* [10] reported that the benefit of adjuvant cyclophosphamide was observed only in the surgical series of patients who received treatment immediately after operation and not in the subgroup of patients (the radiological series) who received cyclophosphamide only after the completion of RT, i.e. about 6 weeks after operation. A number of trials are now analyzing the benefit of preoperative chemotherapy.

Six studies (Table 9) have analyzed the relation between recurrence-free survival and duration of therapy. In the first study from Milan [16] 6 cycles of CMF were compared with 12 cycles. At 4 yr recurrence rates in the two groups were 30.6 and 37.3% respectively. Analyzed in relation to menopausal status and number of involved nodes, the same trend was apparent in all subgroups, but the difference did not reach statistical significance.

The results from two other studies, one also comparing 6 cycles with 12 cycles of CMF [36] and one comparing 5 cycles with 10 cycles of AC (37), both confirm the results from Milan.

Reports of another two trials have been published. Preliminary results from the first trial [38, 39] indicate 12 cycles of CMF to be superior to 1 cycle. In the other trial [40] efficacy of adjuvant LMF was observed only in node-negative patients. In these patients no difference was observed between 6 and 24 cycles of LMF. Finally, one study comparing 1 with 2 yr of treatment with CMFVP has been published [41]. This is still ongoing and as yet no results are available.

Relation between drug dose/drug-induced toxicity and RFS

The relation between drug dose and RFS has been analyzed retrospectively in a number of studies [19, 33, 42–44]. In the first study, published by Bonadonna and Valagussa [44], the RFS was reported to be significantly related to the dose level in both pre- and postmenopausal patients, and the lack of efficacy of adjuvant CMF to postmenopausal patients was ascribed to the fact that the majority of these patients received inadequate doses.

Table 10. Relation between dose level/toxicity and relapse-free survival

Reference	Treatment	*n*	Follow-up time (yr)	Dose level/ toxicity level	*n*	RFS, in favor of:
[42]	RT + CMF, 1 yr	102	4	65–84%	NI	Pre: N.D.
				≥85%	NI	Post: highest dose ($P = 0.15$)
[33]	L-PAM, 2 yr	61	3	WBC <3000	27	Pre + Post: lowest dose ($P = 0.013$)
				WBC ≥3000	34	
[33]	CMF, 2 yr	33	3	WBC <3000	23	Pre + Post: N.D.
				WBC ≥3000	10	
[19]	L-PAM, 2 yr	187	3–7	<90%	45	Pre + Post: lowest dose ($P = 0.07$)
				≥90%	142	
[43]	RT + C, 1 yr	145	3	<75%	90	Pre: highest dose ($P = 0.065$)
				≥75%	55	
[43]	RT + CMF, 1 yr	167	3	<75%	88	Pre: lowest dose ($P = 0.24$)
				≥75%	79	

Conflicting results have been reported in other studies which are summarized in Table 10. One study with adjuvant CMF [42] confirmed the Milan findings in post- but not premenopausal patients. In two studies with adjuvant L-PAM the recurrence rates were highest ($P = 0.07$) in patients treated with the highest doses [19] or who experienced the highest ($P = 0.0131$) WBC toxicity level [33]. Another two studies with adjuvant CMF [33, 43] and one with cyclophosphamide [43] failed to demonstrate any significant relation between drug dose and RFS.

In conclusion, the available data are conflicting. This may partly be ascribed to different regimens and definitions of dose levels.

Also, these retrospective analyses may well be invalidated by factors not related to the dose level as such but to the fact that patients at greatest risk of recurrence are less able to tolerate the drugs and thus require a more pronounced dose reduction than low-risk patients. Additional prospective trials are needed to enable safe conclusions.

It has been argued that some of the effects of adjuvant chemotherapy given to premenopausal patients might be attributed to drug-induced ovarian suppression. However, the results from three studies [19, 45, 46] indicate that the RFS is not related to ovarian suppression. Thus in the study from Milan [45] 5-yr relapse-free survival rates were identical in patients with and without amenorrhea during CMF treatment in the two age groups studied ($\leqslant 40$ and >40 yr). Similarly, 4-yr data from the NSABP study with control vs L-PAM [46] showed no relation between benefit of L-PAM and occurrence of amenorrhea, and the same experience was reported from another study, also using L-PAM [19].

ADJUVANT IMMUNOTHERAPY WITH OR WITHOUT CHEMOTHERAPY

A number of randomized trials have evaluated the efficacy of adjuvant immunotherapy. In the trial conducted by DBCG [47] the early rate of recurrence was increased in the group of patients treated with levamisol compared to the control group. In another two trials the addition of levamisol to CMF [48] or to AC [49] had no effect on RFS compared to chemotherapy alone. Another four randomized trials failed to demonstrate any benefit of BCG when given either together with adjuvant chemotherapy [50, 51] or after the completion of the chemotherapy [52, 53].

In a study from France [54] 300 node-negative and -positive patients were randomized to adjuvant placebo or to weekly injection of Poly A–Poly U, (polyadenylic–polyuridylic acid) continued for 6 weeks. After 5 yr RFS was identical in the two groups but in the node-positive patients a significantly increased RFS ($P \leqslant 0.03$) was observed in the Poly A–Poly U-treated group.

Thus adjuvant therapy with levamisol or BCG, whether given alone or in combination with chemotherapy, does not improve the RFS, but the possible advantage of Poly A–Poly U should be confirmed by other investigators.

ADJUVANT CHEMOTHERAPY WITH OR WITHOUT POSTOPERATIVE IRRADIATION

Three non-randomized [25, 55, 56] and five randomized [20, 32, 36, 57, 58] studies of radiotherapy with or without adjuvant chemotherapy have been published. The results are conflicting, but all these studies have recruited rather small numbers of patients and the follow-up time is still very short. The available data fail to demonstrate any significant trends, but different surgical procedures, adjuvant chemotherapy regimens and time sequences of the radiotherapy and chemotherapy in the different studies and lack of distinction between rates of local and systemic recurrence impede the comparison of results. Hopefully this very important question will be answered in ongoing and future randomized trials.

Only one trial has directly compared adjuvant chemotherapy (CMF) with radiotherapy [59] and no difference in recurrence rates has so far been observed.

PART 2. ENDOCRINE THERAPY

RATIONALE

Endocrine ablative and additive therapy in advanced disease gives an overall response rate of 30–40% [60–64]. Since the demonstration of estrogen receptor protein in tumor cells by Jensen and other investigators [65–67], this therapeutic effect can be correlated to a measurable index of hormone responsiveness of recurrent disease. It has been confirmed that approximately 50% of ER+ and 10% of ER- tumors respond to endocrine therapy in advanced disease [68–72] and that the response rate is proportional to the amount of receptor protein measured [73, 74].

Due to the frequent inaccessibility of recurrent metastatic lesions for ER biopsy, the correlation of the response in advanced disease often has to be based on receptor measurement of the primary tumor. However, several studies [75, 76] with sequential tumor biopsies from the same patients have shown that the ER status of the primary and recurrent tumor is unchanged in about 85% of cases. It can therefore be assumed that the ER status of the primary and recurrent tumor reflects to a high degree the ER status of the micrometastases left after primary local therapy.

These results also indicate that the tumor population of the primary tumor, the micrometastases and the recurrent tumors should be regarded as heterogeneous, being composed by clones of both ER+ and ER- cells. The ER status of a measurable lesion is therefore an expression of the dominance of either ER+ or ER- tumor cells in that particular tumor and may be different to that of concomitant or recurring tumors. This is important when responsiveness of non-measurable micrometastases is correlated to the ER content measured in the primary breast tumor.

The action of endocrine therapy cannot in general be described by kinetic terms as for cytotoxic agents, but from therapy of large volume tumors experience suggests that response to endocrine therapy occurs more slowly than with chemotherapy. The mechanism of action of endocrine therapy is based on the reduction of steroid hormones of ovarian and adrenal origin capable of stimulating tumor growth, endocrine agents inhibiting growth stimulation by other hormones mediated through hormone receptor in the tumor cells, as evidenced by the receptor/response relation [68–72] and the decrease of receptor protein content in tumors responding to endocrine therapy [75, 76], or, possibly, a direct cytotoxic action.

Breast cancer is known to be heterogeneous [77–81] but, as opposed to endocrine therapy, the effect of cytotoxic therapy seems to be unrelated to the ER status [82–84]. Therefore it is rational to combine chemotherapy and endocrine therapy in the adjuvant treatment of breast cancer.

CLINICAL APPLICATION

Endocrine therapy alone or in combination with cytotoxic regimens have been investigated extensively during the last decade in adjuvant trials. At present only a few, still preliminary results are available concerning additive therapy. These data and the conclusive results of primary castration will be considered and related to prognostic factors and to estrogen receptor status of the primary disease.

PRIMARY CASTRATION IN OPERABLE BREAST CANCER

Recurrence and survival data at 10 and 15 yr

The efficacy of primary castration has been investigated in a few trials including a non-treated control group. In 1948 a randomized study was initiated at the Christie Hospital in Manchester with 596 premenopausal patients, and 5-, 10- and 15-yr results have been published [85–87].

In 1957 a series of adjuvant studies were initiated by Nissen-Meyer, investigating the efficacy of ovarian irradiation, surgical oophorectomy and the addition of prednisone in prognostic subgroups of pre- and postmenopausal patients. Two of these investigations were not randomized or did not include a non-treated control group [88], and only the controlled studies will be considered [88–90].

In the Toronto trial conducted by Meakin *et al.* [91–93] a total of 779 patients were randomized over a 7-yr period beginning in 1965. Premenopausal patients less than 45 yr old were randomized to receive either ovarian irradiation or no further therapy, whereas premenopausal women older than 45 yr and postmenopausal women were randomized to receive ovarian irradiation and prednisone (7.5 mg daily) for 3 yr.

Ten- and 15-yr analyses of both the Oslo and Toronto studies conclude that statistically no benefit can be observed in the postmenopausal patients. All three studies also concluded that premenopausal patients do not benefit significantly from ovarian irradiation. In the Manchester study a subgroup of older premenopausal node-positive patients had a significant reduction in rate of recurrence, and in the Oslo study including node-negative patients an inconsistent significant decrease in rate of recurrence was reported.

The effect of ovarian irradiation is not far from a statistically significant level both on rate of recurrence and survival in the Toronto trial, where in premenopausal women less than 45 yr old there was a trend towards improvement, with P values of 0.13 and 0.19 respectively. The addition of prednisone to ovarian irradiation in premenopausal patients older than 45 years in the Toronto study led to a significant increase in rate of RFS and survival at both 10 ($P = 0.02$ and 0.02 respectively) and 15 yr ($P = 0.04$ and 0.02 respectively) [93].

Table 11. Trials of adjuvant tamoxifen +/- chemotherapy

Study group	Abbreviation	Reference
Nolvadex adjuvant Trial Organisation	NATO	[106]
Copenhagen Breast Cancer Trials	CBCT	[100]
Danish Breast Cancer Cooperative Group	DBCG	[105]
Stockholm-Gotland Oncologic Center	ST-G	[59]
Case Western Reserve and other centers	CWR	[104]
National Surgical Adjuvant Breast Project	NSABP	[107]

Despite the limited number of patients in each prognostic subgroup, it can be concluded that primary castration in both node-negative and -positive premenopausal patients prolongs the disease-free interval and increases the RFS and overall survival. The significant effect of combined castration and prenisone therapy in an age-subgroup of premenopausal node-negative and -positive patients needs to be confirmed by other investigations. A number of trials are in progress to evaluate the efficacy of primary castration and the correlation of any effect to estrogen receptor status.

ADJUVANT TAMOXIFEN ALONE AND COMBINED WITH CHEMOTHERAPY

The efficacy of tamoxifen in advanced disease and correlation to ER status has been confirmed in numerous studies [94–98], and combined with chemotherapy is superior to chemotherapy alone [99]. In general only a few, mild side-effects are recorded during long-term therapy with this agent [96, 98].

TREATMENT RESULTS

RFS data

Few and only preliminary results have been published from a large number of ongoing trials (Table 11). In only two studies [100–104] have all patients been observed for at least 5 yr; in the rest the median time of observation ranges between 17 and 29 months. Survival data have therefore not yet been reported from the majority of these trials.

The reduced rate of loco and/or regional recurrences in patients receiving postoperative radiotherapy in the first years should be taken into account if these preliminary results of the individual trials are to be compared. In the CBCT and DBCG study all patients received radiotherapy, whereas only high-risk patients (N+, or T $\geqslant$ 3 cm) and those N+ with axillary node sampling surgery in the ST-G and NATO trials, respectively, received radiotherapy. Because only the data of the NATO study specify the individual rate of loco-regional and distant recurrences, it is not possible to compare the rates of distant metastases in these studies.

Table 12. Trials of adjuvant tamoxifen including a non-treated control group

Study group	No. of patients	Menopausal status	Age limit (yr)	Node status	Daily dose (mg)	Treatment duration (yr)	Median observation time (months)	Statistical significance
NATO	1098	Pre		N+	20	2	21	yes ($P = 0.01$)
		Post	75	N–, +				
							78	yes ($P = 0.015$)
CBCT	336	Pre, Post	70	-	30	2		
							17	no ($P = 0.19$)
DBCG	1247	Post	80	N+	30	1		
							29	yes ($P = 0.01$)
ST-G	582	Post	70	N–, +	40	2		

Table 13. Chemotherapy with and without tamoxifen

Study group	Regimen	No. of patients	Menopausal status		Age		Treatment duration	Median observation time (months)	P value for RFS in favor of T
			Pre	Post	≤49 yr	>50 yr			
CWR	CMF	99	95	217 (76 yr)			CMF, T:1 yr BCG second year	63	0.02
	CMF+T & CMFT+BCG	213							
NSABP	PF	927			392	535	2 yr	24	0.02
	PF+T	936			388	548			

T = tamoxifen

Table 14. RFS in relation to menopausal status and age

Study group	Median observation time (months)	No. of patients	Menopausal status, age group	Statistical significance	Significant effect on RFS
NATO	21	127	Pre	Yes	yes
		971	post	yes	
CBCT	78	217	Pre	no	yes
		119	Post	yes	
DBCG	17	1247	Post, 50–59 yr	yes	no

Table 15. RFS in relation to menopausal status and age

Study group	Regimen	Median observation time (months)	*P* value for RFS in favor of T			
			Pre	Post	≤49 yr	>50 yr
CWR	CMF CMF+T	63	0.06	0.04		
NSABP	PF PF+T	24			0.9	0.001

At present the general trend demonstrated in the endocrine studies including a non-treated control group and in the two studies with a chemotherapeutic control group indicate that the initial effect of tamoxifen is a significant decrease in the rate of recurrence (Tables 12, 13).

EFFICACY OF ADJUVANT ENDOCRINE THERAPY IN RELATION TO PROGNOSTIC FACTORS

Menopausal status

Pre- and postmenopausal patients were treated with the same regimen in three studies (Tables 13–15). In the CBCT trial [100, 101] the overall rate of recurrence of TNM stage I–III patients was significantly reduced by tamoxifen ($P = 0.015$), but when dividing into menopausal subgroups the effect was significant only in postmenopausal patients ($P = 0.004$), whereas in premenopausal patients the clinical effect did not reach statistical significance ($P = 0.31$). In the NATO trial [106] the efficacy of tamoxifen was not significantly related to the menopausal status, and in the CWR study [50, 102, 105] the combination of CMF + T was superior to CMF alone with regard to RFS at 5 yr ($P = 0.02$), and this difference was apparent in both pre- and postmenopausal patients ($P = 0.06$ and 0.04 respectively). The efficacy of adjuvant tamoxifen therefore does not seem to be significantly related to the menopausal status of the patient.

Age

A life table analysis at 36 months of 1247 high-risk (N+ or T > 5 cm or invasion to skin or fascia) postmenopausal patients in the DCG study (Table 14) demonstrated a decrease of 9% ($P = 0.19$) in rate of recurrence of all patients treated with tamoxifen. In patients 50–59 yr old the reduction of recurrence rate was statistically significant ($P = 0.025$).

The combination of PF + T (L-PAM + 5-fluorouracil and tamoxifen) in the NSABP study [107] is overall significantly superior to therapy with PF alone ($P = 0.02$) among 1863 pre- and postmenopausal patients (Table 15). In this study patients were grouped according to age. In 780 patients aged less than 49 yr the effect of PF + T on RFS was not significant ($P = 0.9$), nor was it so in any prognostic subgroup, whereas the effect was highly significant in 1083 patients over 50 yr of age ($P = 0.001$). These results seem to conflict with the beneficial effect of CMF + T in both pre- and postmenopausal women [104]. A possible explanation of this discrepancy has been offered by the authors of the CWR trial referring to the short time of observation in the NSABP study and to the fact that the efficacy of ovarian irradiation and prednisone in premenopausal patients in the

Table 16. RFS in relation to node status and ER-status

Study group	Median observation time (months)	No. of patients	Menopausal status	Significant difference N-	N+	N_{1-3}	N_{4+}	ER status
NATO	21	127	Pre	—	yes	yes	yes	no
NATO	21	971	Post	yes	yes	yes	yes	no
DBCG	17	1247	Post	—	no	no	yes	no
ST-G	29	582	post	yes	yes			yes
CBCT	78	336	Pre, Post					no

Table 17. RFS in relation to number of positive nodes

Study group	Regimen	Menopausal status, age group	*P* value ALL N+	No. of nodes 1-3	4+
CWR	CMF CMF+T	Pre, Post	0.02	0.45	0.025
NSABP	PF PF+T	>50 yr ≤49 yr	0.001 N.S.	0.18 N.S.	0.001 N.S.

Toronto trial was not significant until 3–5 yr after mastectomy [108].

Node status

In both the NATO and ST-G trials [59, 106] the significant effect of tamoxifen on RFS is observed in both node-positive and -negative postmenopausal patients, and in the first study the effect on node-positive patients was not significantly related to the number of positive nodes (Table 16). This was, however, observed in the DBCG trial, where only postmenopausal patients with more than four positive nodes demonstrated a significant beneficial effect of therapy with tamoxifen. Axillary node status was not analyzed in the CBCT trial. A therapeutic relationship to the number of positive nodes is clearly demonstrated in the chemotherapeutic trials (Table 17). Thus CMF + T was not significantly superior to CMF alone in either pre- or postmenopausal patients with 1–3 positive nodes ($P = 0.45$) whereas the effect was significant in all patients with ≥4 nodes ($P = 0.025$). In the NSABP study of patients older than 50 yr the overall effect on RFS in patients with ≤3 nodes was not significant ($P = 0.18$), but in the subgroup with ≥4 positive nodes the efficacy of PF + T was significantly superior to PF alone ($P = 0.001$).

In the CWR trial the rate of recurrence in patients with 1–3 positive nodes treated with CMF + T was lower than in the CMF control group during the first 2½ yr, but thereafter the rate of recurrence in the CMF + T group exceeded that in the CMF group [104]. This observation may indicate a regrowth of hormone-sensitive tumors in which a relatively slow rate of growth is not effectively inhibited by treatment with tamoxifen during 1 yr. As a result of these data another adjuvant study designed by this group has been activated in which ER+ patients receive tamoxifen for 3 yr.

ER status

The estrogen receptor status of the primary tumor was measured in the majority of patients included in previously mentioned trials, but only in the CWR study was this a criteria for entry. No significant correlation between therapeutic effect of tamoxifen and receptor status was observed in the CBCT and NATO trials, either in pre-menopausal or in postmenopausal patients (Table 16). The results of the NATO study is, moreover, based on correlations to different levels of receptor protein. In the first report of the DBCG study data are still very preliminary.

In the ST-G study of both node-negative and -positive postmenopausal patients, tamoxifen only decreased the rate of recurrence significantly in ER+ patients, and correlation of this effect to level of receptor protein has recently been reported [59].

In the two chemotherapeutic studies the correlation between responses to ER status has been extensively analyzed in different prognostic

subgroups. As shown in Table 18, the therapeutic effect of CMF + T was only significantly superior to CMF in ER+ patients with ≥4 nodes involved ($P = 0.05$), whereas no significant effect was observed in either ER+ with 1–3 nodes involved ($P = 0.97$) or in ER– patients. The results of the NSABP study (Table 15) also indicate that the effect of tamoxifen added to chemotherapy was significant only in ER+ patients with ≥4 positive nodes, whereas in agreement with the results of the CWR study, no significant effect ($P = 0.5$) was observed in the ER+ patients over 50 yr with 1–3 nodes involved. When the effect was related to the level of receptor protein it was apparent that in patients with 1–3 positive nodes the P value increased to a non-significant level if the tumor contained less than 40 fmol of receptor protein. In patients with 4 or more positive nodes, however, the effect of PF + T was highly significant in tumors with more than 10 fmol ($P < 0.001$).

In conclusion, although the available data are preliminary results and partly inconsistent, it seems that the efficacy of adjuvant tamoxifen is related to the presence of the estrogen receptor in the tumor tissue. A longer follow-up period in the ongoing trials is needed to define this relation exactly, and future studies should also define the predictive therapeutic importance of the level of the receptor protein.

DURATION OF THERAPY

The majority of studies have used 1–2 yr of adjuvant tamoxifen and to date no randomized trials analyzing the duration of therapy have been published; however, a number of trials are in progress. Provided that the effect of adjuvant tamoxifen is related to the presence of estrogen-receptor protein in the tumor tissue, and taking into account that the early rate of recurrence in ER+ tumors is very low [109], this therapy should theoretically be sustained for a very long period of time. This has also been indicated in experimental studies [110] showing that the tamoxifen therapy should be continued for a long period of time in relation to the life span of the host in order to prevent the regrowth of dormant tumor cells.

DISCUSSION AND CONCLUSIONS

Clinical data indicate that breast cancer is already a systemic disease at the time of diagnosis, and experimental data have shown that the possibility of curing a tumor-bearing organism increases with decreasing tumor burden. These data together with the proven efficacy of cytotoxic and endocrine therapy in advanced disease indicate that systemic adjuvant therapy theoretically represents the best chance of improving the prognosis in breast cancer.

Only a limited number of randomized trials of adjuvant chemotherapy including a no-treatment group have been published. The early trials, now with 5–10 yr of observation, demonstrate a therapeutic effect measured as prolongation of RFS, and preliminary data also indicate a survival gain in some subsets of patients.

Following these initial trials an extensive number of adjuvant studies have been published. Unfortunately most of these studies do not include a no-treatment control group. Many of them have recruited an inadequate number of patients, or the time of observation is still too short to allow any firm conclusions.

The available data indicate that the major early benefit of adjuvant therapy is confined to high-risk patients. However, this observation may be attributed to the fact that the times of observation are still very short and limited to the very early phase of the course of the clinical disease. The results from large controlled trials with prolonged time of observation will hopefully improve the criteria of selection of patients who should benefit from adjuvant chemotherapy.

The optimal duration of the therapy remains undefined, but limited data indicate that the maximum cytoreductive effect is achieved within the first few months after mastectomy. Also, preoperative chemotherapy is now being considered.

Although the available data are inconsistent, it seems that combination chemotherapy is superior to single agents. Retrospective analyses of recurrence rates in relation to drug doses are conflicting, and ultimate conclusions will require

Table 18. RFS in relation to estrogen receptor status (P values given)

Study group	Regimen	Menopausal status, age group	ER-positive			ER-negative
			OVerall	No. of nodes 1–3	4+	
CWR	CMF CMF+T	Pre, Post	0.01	0.97	0.05	N.S.
NSABP	PF PF+T	>50 yr ≤49 yr	0.002 N.S.	0.5 N.S.	0.001 N.S.	0.1 N.S.

prospective studies relating recurrence rates to both drug dose and hematological toxicity.

The present status of adjuvant endocrine therapy is very similar to that of chemotherapy, and only a limited number of trials offer conclusive data. Although the results are somewhat conflicting, randomized clinical trials of adjuvant ovarian ablation or irradiation have demonstrated a difference in recurrence rate and survival in favor of the treated group. This difference, however, only reaches statistical significance when prednisone is added to the treatment.

Since 1974 the efficacy of tamoxifen as a systemic adjuvant agent has been investigated in a large number of trials. Data from these studies indicate that tamoxifen, either as a single agent or in combination with cytotoxic agents, can lead to a prolongation of the disease-free interval. Only a few trials incorporate other endocrine agents, and results from these trials are not yet available.

It is probable that the steroid receptor status will appear to be an important predictive factor as to the efficacy of the endocrine therapy, but the results are still preliminary and do not at the present time permit any firm conclusions.

In conclusion, the ultimate effective adjuvant systemic regimen has yet to be demonstrated, and since the superiority of one particular treatment is not evident, such therapy must still be considered experimental and should be administered within the framework of prospective clinical trials. These trials should also further analyze prognostic factors and predictive tests for the efficacy of the treatment, the proper drugs or combinations of drugs, the time for and duration and intensity of therapy, and the acute and long-term toxicities. The trials should also include studies of the psychological and socio-economic implications of adjuvant systemic therapy.

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