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Adjuvant Therapy of Breast Cancer

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Adjuvant systemic therapy has been shown to reduce relapses in treated women and to prolong their survival. This is true for all studied subpopulations. Multidrug chemotherapy for the duration of 6 months for the premenopausal patients, and tamoxifen or short-term chemotherapy with long-term tamoxifen for the postmenopausal patients represent the treatments of choice to reduce the risk of relapse. Some of the high priority questions relate to i) the definition of a population for which the risk of relapse is low enough to avoid the use of systemic adjuvant therapy, and ii) the definition of an optimal way of using available adjuvant therapies. These might find answers from ongoing research. The modest but real improvement of the prognosis in operable breast cancer was exclusively obtained only by means of clinical trials, and it is mandatory that participation in programs of clinical research becomes medically and socially the treatment of choice.
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INTRODUCTION

MOST BREAST cancer patients who remain disease-free after local and regional treatment eventually relapse and die of or with overt metastasis. This is true regardless of whether they received an appropriate local therapy. The current hypothesis ascribes the failure to obtain freedom from disease to occult micrometastatic disease already present at the time of diagnosis and first surgery [1]. This hypothesis has acquired indirect support from the results of clinical trials which show no additional advantage in terms of disease-free or overall survival for a more radical local therapy [2, 3].

There is evidence that occult metastases can still be eliminated by current therapeutic means, but that the overt metastatic phase of the disease is incurable. These observations lead in turn to substantially different attitudes towards the treatment of patients in these two distinct clinical situations.

Long before the present hypothesis of disease spread (presence of micrometastases at diagnosis), adjuvant systemic therapy was applied in a form of hormonal ablative treatment consisting of ovarian radiation [4]. At that time, observations made of tumour regression after oophorectomy justified investigation of ablative therapy in patients with operable disease after completion of the local treatment.

Systemic adjuvant chemotherapy was based upon observations of substantial rates of response to cytotoxic agents of measurable metastatic disease. In addition, the first hypothesis concerning their value as adjuvant treatment was related to the attempt to kill cells which detach during operation. The detached cells were at that time considered to be responsible for the subsequent development of overt metastases. This hypothesis of perioperative migration of cells with metastatic potential has been abandoned in favour of one which argues for the presence of micrometastatic disease at the time of primary diagnosis [5].

Experimental observations which have helped to guide the use of adjuvant systemic therapy after surgical removal of the primary tumour have been made on the basis of animal models [6–10]. There is an inverse relationship between the number of viable tumour cells in the animal and response to treatment with cytotoxic agents, i.e. the smaller the number of tumour cells the greater the chemotherapeutic effect. Another principle related

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to the effectiveness of adjuvant systemic therapy relates to its time of application. It indicates that if the surgery has reduced the number of cells to micrometastases consisting of no more than 100 cells, the optimal time for chemotherapy potentially to eradicate all cells is immediately after operation. In fact, adjuvant therapy after surgery will increase the cure rate in animal models in contrast to both delayed administration of drugs and their use without surgical tumour reduction [11]. In an attempt to explain the failure of adjuvant therapy to achieve cure in most of the treated humans despite the fact that a first-order kinetics drug action might have predicted otherwise, the following issues arise.

(i) Tumour heterogeneity as related to the cell cycle, cellular metabolism, and the drug availability within a tumour mass.
(ii) Resistance to treatment. Among the causes for drug resistance, which may be intrinsic or acquired, are some which are related also to the timing of the drug administration. In fact, early administration of cytotoxic drugs, based upon an experimental system is hypothesised to prevent the development of resistant tumour cells [12].
(iii) The growth of tumour cells is hypothesised to follow Gompertian kinetics in which plateaux of slow or no growth are interrupted by random growth spurts [13]. These spurts may be favoured by treatment-free intervals, and represent periods of higher susceptibility to cytotoxics. According to this latter hypothesis the most effective treatment to prevent metastasis is that which follows therapy-free intervals.

ADJUVANT SYSTEMIC THERAPY

Irrespective of the foregoing considerations which describe our theoretical knowledge about why and how systemic therapy might or might not function, its application in operable breast cancer roughly followed an empirical pathway. All the knowledge related to the benefits of adjuvant systemic treatment is derived from randomised trials. The trials, designed to define treatment benefit in terms of disease-free survival (DFS) or overall survival (OS), were focused upon the type of therapies which were believed likely to produce an improvement of outcome.

The following main types of treatments (and some related details) have been investigated over the past 45 years.

(i) Adjuvant oophorectomy (either surgical or radiation-induced).
(ii) Adjuvant perioperative cytotoxic therapy of short duration (given immediately after completion of surgery of the primary tumour).
(iii) Adjuvant prolonged chemotherapy: mainly studied in patients with axillary node metastases (N+); role of a multidrug combination chemotherapy as opposed to a single agent; duration of treatment; timing of treatment; and definition of "dose intensity" of chemotherapy.
(iv) Adjuvant endocrine therapy mainly with prolonged administration of the antiestrogen tamoxifen; endocrine therapy compared with chemotherapy; response to treatment by oestrogen (ER) and progesterone receptor (PR) content in the primary tumour.
(v) Adjuvant chemoendocrine therapies.

Some trials were specifically conducted in a risk-adapted fashion to allow also patient-oriented questions to be answered, [i.e. trials in "lower-risk" patients with no axillary node metastases (N−); trials accruing only patients with known oestrogen receptor content in the primary tumour ER+ or ER− tumours].

*Table 1. Review of randomised trials of adjuvant therapies according to the type of treatments investigated**

Trial design	No. of trials	No. of patients
Oophorectomy vs nil	8	2968
Perioperative vs nil	15	>7000
Postoperative CT vs nil (N+)	31	>7000
CT vs adjuvant RT	8	>2200
Multi vs single agent CT	15	>4000
Perioperative vs postoperative CT	6	>1200
Preoperative vs postoperative CT	3	>500
Two multidrug regimens	17	>5000
CT ± RT vs CT	6	>1000
Two chemotherapy durations	9	>3000
Early + late CT vs early	3	>2000
Two chemotherapy doses	3	>500
Tamoxifen vs nil	27	>10 000
Two tamoxifen durations	7	>1500
Two endocrine therapies	3	>500
CT vs endocrine therapy	12	>3000
Other endocrine vs nil	5	>600
Chemoendocrine vs nil	8	>1200
Endocrine vs chemoendocrine therapy	18	>2500
CT vs chemoendocrine therapy	25	>8000
Postoperative CT vs nil (N−)	17	>4500
Chemoendocrine vs CT or endocrine (by ER)	2	>1000

*Modified from ref. 14 (not all trials are published).
CT = chemotherapy, RT = radiotherapy.

Table 1 lists the types of therapeutic questions by number of trials and number of patients [14] (modified).

Adjuvant oophorectomy

An example of a trial comparing surgical oophorectomy to no adjuvant treatment is the Saskatchewan trial in which, from 1964 to 1973, 359 women (46% of whom were N+) were randomly assigned to one of the two treatment options [15]. While after 5 years of follow-up the difference between the two treatment groups was significant only in terms of DFS (8% difference, $P < 0.05$), after 10 years an overall survival advantage in favour of the oophorectomy group also appeared, and the difference increased to 11% ($P < 0.05$). The delayed appearance of a difference in outcome for endocrine-treated patients seems to be a pattern common to the trials with ablative endocrine therapies.

Adjuvant perioperative chemotherapy

An example of a trial comparing a short course of perioperative chemotherapy is Trial V of the International Breast Cancer Study Group (IBCSG; formerly the Ludwig Group) [16]. Between 1981 and 1985, 1275 patients with N− breast cancer received either a single course of cyclophosphamide (C), methotrexate (M) and 5-fluorouracil (F) or no adjuvant therapy. At 5 years median follow-up the 5-year DFS percentages were 74% for the adjuvant therapy group as compared to 68% for the controls (relative reduction in the risk of relapse of 22%; $P = 0.02$). The largest magnitude of effect was shown for patients who had low or no oestrogen receptor levels in the primary tumours (ER−). The differences were seen for pre- and postmenopausal patients and the treatment may be considered effective although additional

Table 2. Median DFS and OS at 12 years for patient randomised to one year of CMF or no adjuvant therapy (control) in the Milan Trial

	Median DFS (mo)		Median OS (mo)	
Patient group	Control	CMF	Control	CMF
All	40	83	104	140
N+				
1–3 nodes	63	141	130	Not reached
4 or more	20	44	77	82
Premenopausal	32	141	96	Not reached
Postmenopausal	59	64	128	113

courses of systemic adjuvant therapy were proven to increase the benefit in a cohort of 1229 patients with N+ disease within the same trial [17].

Adjuvant prolonged chemotherapy

The Milan trial is an example of a study comparing prolonged chemotherapy (12 courses of CMF) to surgery alone, and is considered one of the hypothesis-generating investigations in the field [18]. Table 2 illustrates the highly significant difference for the premenopausal patients in contrast to the similar outcomes for both treatment groups in the postmenopausal populations. The lack of effect of the treatment program in postmenopausal women has been attributed to the lower doses of cytotoxics given to the older women in the trial. The issue of chemotherapy rather than endocrine therapy or combined chemoendocrine therapy for postmenopausal patients remained controversial until recently, when some large-scale trials showed the increased benefit from the combined regimen as compared to endocrine therapy alone. Additional evidence is needed to better define the magnitude of the effect in risk-adapted settings (i.e. groups selected by the oestrogen receptor content in the primary tumour).

The trials in which a single-agent chemotherapy was compared to a multidrug combination indicate, together with data from indirect comparisons, that combination therapy is likely to yield a significantly greater benefit in terms of outcome, especially for premenopausal patients. The cyclophosphamide, methotrexate, 5-fluorouracil combination (CMF) has been compared with the same combination plus either low-dose continuous, or high-dose intermittent prednisone (p or P), and to a drug combination which includes vincristine given weekly (CMFVP), but no advantage in favour of the 4- or 5-drug regimens has been demonstrated.

Comparisons of doxorubicin-containing regimens with other multidrug combination therapies were based upon the observations in advanced disease. Their application was associated with higher response rates although differences in overall survival were rare. Results are available from three studies in which a doxorubicin combination was compared with a combination chemotherapy of the same duration which did not contain it. In all of the trials the addition of doxorubicin to the combination was associated with a significant improvement in the DFS and, of minor magnitude, in overall survival too. In all three trials, however, other important variables were also included: a non-randomised addition of radiation therapy, the addition of a hormonal agent—fluoxymestrone acetate—added to the combination in the second trial, and the application of the anthracycline in the middle of the treatment course (i.e. after 3 weeks from last administration of cytotoxics), completely changing the schedule in comparison to the control regimen (L-PAM and 5-fluorouracil given every 6 weeks). In a recent trial for premenopausal women (and some postmenopausal patients with hormone receptor-negative primaries) the use of 4 cycles of doxorubicin and cyclophosphamide was compared to 6 cycles of CMF combination chemotherapy and found to yield equivalent results in terms of disease free survival and overall survival [19]. On the other hand, the routine introduction of doxorubicin into adjuvant therapies, especially for "intermediate risk" populations (i.e. few positive axillary nodes) is regarded by some as incautious in view of its potential long-term cardiac toxicity, and of the need to maintain this most active agent as a reserve to palliate symptoms in case of need.

It is commonly believed that the higher the dose of cytotoxic drugs, the more effective the treatment. This is based upon the increased complete response rates in trials investigating dose-response relationship in advanced breast cancer, even though such high-dose therapies do not imply cure. Retrospective analyses have been performed upon different data sets in an attempt to correlate either failure of response to a given treatment with the lower dose, or the success of a therapy with the higher doses. Respective comparisons of outcome, in fact, show a direct correlation between dose and both disease free survival and overall survival. Due to the retrospective feature of the analysis one might argue that, although the direct relationship may be demonstrated, the cause-effect relationship might be different (i.e. patients who have a less aggressive disease tolerate more cytotoxics). The only way to learn whether there is indeed a dose-response relationship within the ranges of the described doses is to directly compare two dose levels in a prospective randomised trial. Such trials are currently being conducted by several groups.

Two trials are typical of those which addressed the question of duration of adjuvant cytotoxic therapy. The first is the Milan study of 6 vs 12 courses of CMF in which 459 N+ breast cancer patients were included [18]. The 10-year results show an advantage in favour of the shorter treatment course (10-year DFS percentage; 46% for the 12 courses as compared to 53% for the 6 courses). Based upon this trial the most efficacious duration of adjuvant cytotoxic therapy is considered to be 6 courses.

The second trial is related to the hypothesis that the first course, if given perioperatively (immediately after surgery) might yield results in terms of outcome similar to those of the therapies of longer duration. This was partially based on the observation of the Scandinavian Breast Cancer Study Group which identified a significant improved outcome obtained with a perioperative 6-day course of cyclophosphamide [21]. Trial V of the International Breast Cancer Study Group (IBCSG) [22] showed in a population of 1229 patients with positive axillary lymph nodes that one course of chemotherapy is significantly inferior to the prolonged treatment of 6–7 months in terms of both DFS and overall survival. The recent National Surgical Adjuvant Breast and Bowel Project (NSABP) study of doxorubicin plus cyclophosphamide given every 3 weeks for 4 times compared to the 6-months duration CMF showed, as previously mentioned, an equivalent outcome for the two regimens [20].

Studying the question of timing of adjuvant chemotherapy has entailed important practical and logistical challenges. Non-randomised presurgical chemotherapy has been studied under a

variety of clinical conditions but has not yielded convincing evidence of benefit greater than that achieved with the established mode of therapy administered only after surgical removal of the primary and axillary nodes. In a recent series, chemotherapy was given uniformly to patients with large tumours (3 cm or larger) to reduce tumour size and thus make breast conservation possible [19]. In this study more than 90% of the patients were enabled to have a less-than-mastectomy procedure. Preoperative chemotherapy is being compared to a postoperative administration of cytotoxic drugs in an ongoing NSABP randomised trial using doxorubicin and cyclophosphamide. The results will be of relevance to the question of whether results of adjuvant therapy may be improved by its preoperative use.

The question of whether early administration of chemotherapy (immediately after surgery) might improve outcome as compared to the usual delayed administration (i.e. after removal of stitches and healing of the wound, which is 4–6 weeks) has been addressed in a single randomised trial (Trial V of the IBCSG) [17]. Indirect evident from a study of the Scandinavian Group [21] using a single course of cyclophosphamide alone for 6 days showed that in all participating hospitals where the drug had been administered immediately after surgery there was a benefit in favour of the treated patients. In the only hospital in which, due to referral patterns, the treatment started with a delay as short as 3 weeks, no advantage in terms of DFS or OS could be observed. Trial V showed that no advantage is obtained by starting the adjuvant chemotherapy immediately after surgery compared with the usual delay, provided that six or seven months of adjuvant therapy are administered. The 5-year DFS percentage for the 815 patients with N+ breast cancer who were randomised to early vs delayed administration were 54% vs 53%, respectively. This result, however, does not contradict the Scandinavian Group Trial as a no-adjuvant treatment control was not studied in the N+ subpopulation of IBCSG Trial V.

Delayed and repeated administration of cytotoxic drugs after treatment-free intervals is the subject of recently activated trials [22]. The fact that the same treatment which has been used in the adjuvant setting is eventually effective if used for metastatic disease which appeared after a prolonged treatment-free interval, indicates a lack of definitive resistance of the tumour cells to therapy.

A beneficial effect of adjuvant prolonged (i.e. six-month duration) multidrug chemotherapy in reducing relapse and mortality has been observed in premenopausal patients early during follow-up. Investigations aimed to correlate this effect upon outcome with the amenorrhoea observed in a substantial proportion of the patients, were performed in a number of trials. While the initial research of outcome for patients in the Milan and the NSABP trials with CMF (78 patients), L-PAM alone or with 5-fluorouracil (96 patients) showed no relationship between amenorrhoea and treatment effect, additional analyses, conducted for 1839 patients included in several trials showed some association between the cessation of menses and outcome. The effects of amenorrhoea were also seen almost exclusively in the subpopulation of patients with positive oestrogen receptors. These observations have led to the speculation that adjuvant cytotoxic therapy is effective only because it causes a chemically-induced oophorectomy [23]. The two facts that adjuvant cytotoxic therapy is also effective in patients with tumours having no oestrogen receptors, and that it produces effects which begin to appear early during follow-up have been cited as arguments against a major role for an endocrine mechanism. An extensive analysis of a cohort of 1127 premenopausal breast cancer patients who received one of the following therapies: no cytotoxic therapy, a single short course, or a prolonged chemotherapy (6 or 7 courses) has been conducted [24]. Amenorrhoea was associated with an increased DFS only in the patients with prolonged cytotoxic therapy (387 N+ patients of whom 68% ceased menses); the 4-year DFS percentage was 68% vs 61% for the amenorrhoea and no amenorrhoea groups, respectively ($P = 0.05$). In contrast, the comparison between prolonged chemotherapy and one single course among N+ patients (387 vs 188 N+ premenopausal patients included in IBCSG Trial V [17]) showed a much larger difference in treatment effect: 4-year DFS percentages were 66% vs 38%, respectively ($P < 0.0001$). From this indirect comparison between the size of the effects (prolonged vs short duration chemotherapy, and amenorrhoea vs. no amenorrhoea), one might conclude that although cytotoxic-induced amenorrhoea is associated with a better outcome, it is unlikely that this form of endocrine manipulation is the main mechanism of response to adjuvant systemic chemotherapy in premenopausal women.

Table 3. Median DFS and OS at 8 years for patient randomised to five years adjuvant tamoxifen (TAM) or to no adjuvant therapy and tamoxifen given only upon relapse (control) in the Scottish Trial [25]

Patient group	Median DFS (mo)		Median OS (mo)	
	Control	TAM	Control	TAM
All	73	Not reached	95	Not reached
N−	Not reached	Not reached	Not reached	Not reached
N+	31	84	63	85

Adjuvant endocrine therapy

As an example of adjuvant systemic endocrine therapy with the anti-oestrogen tamoxifen, a trial of adjuvant administration of the drug for at least 5 years compared with the use of the same drug upon relapse is discussed. This study, known as the Scottish Trial [25], included 1312 women, of whom 242 were premenopausal with N− disease, and 1070 were postmenopausal with both N− and N+ breast cancer. There was an advantage in terms of DFS and OS at the end of the 8th year of follow-up, which was statistically significant for the entire population, for the N+ cohort, and for the postmenopausal women. Table 3 describes the differences in the median disease-free and overall survival periods for the two treatment groups at 8 years' follow-up time. This trial is important because it reports a population in which the comparison made is between the same treatments given either as adjuvant or as delayed therapy upon relapse (which was applied in more than 90% of the patients in whom the disease reappeared). The fact that a significant overall survival difference has been demonstrated is indirect evidence that early administration of antineoplastic agents, which fail to achieve cure when applied at the advanced disease stage, may be curative if administered while the tumour burden is low.

The dosage of adjuvant tamoxifen has not been studied. Doses between 20 mg and 40 mg a day have been given in various trials. A recent report of an excess of endometrial cancer in patients who received 40 mg per day for at least 2 years [26] could not be confirmed in an analysis of the Scottish trial in which 20 mg a day was given for 5 years [27]. Assuming

equivalent antineoplastic effectiveness for these two doses of tamoxifen (based upon results from trials in advanced disease), the recommended dose is, therefore, 20 mg a day.

The question of duration of endocrine therapy with tamoxifen has not yet been clarified. Indirect evidence from non-randomised comparisons suggests that the administration of tamoxifen should continue for at least two to five years. This should be the basis for therapy decision-making outside of clinical investigations, at least until the results from randomised studies of five years vs continuous administration become available.

The question of response to adjuvant endocrine therapy according to oestrogen receptor content of the primary tumour is controversial. The controversy is related to the positive effects of tamoxifen seen in retrospective analyses of British trials for patients with ER-primaries [25, 28]. The data from the Trials III and IV of the International Breast Cancer Study Group [29] show that only patients who had ER+ primaries benefit from the endocrine therapy with tamoxifen and low-dose prednisone given for one year. Also in Danish and Canadian trials investigating tamoxifen alone, only the ER+ subpopulation benefited. The response to adjuvant tamoxifen for patients with ER− primaries might, however, be explained by results of recent experiments which related the drug's activity to the production of transforming growth factor β (TGF-β), which inhibits the growth of breast cancer cells regardless of their steroid hormone receptor content [30]. TGF-β is produced in cells containing ER, a fact which explains the importance for response of a heterogeneous population of the tumour cells to treatment of some cellular elements with high concentrations of oestrogen receptors. The definition of benefit from an endocrine treatment alone for the population of patients with ER− tumours, especially those of postmenopausal age, awaits maturation of trials specifically investigating this issue.

Adjuvant chemoendocrine therapies

Combined chemoendocrine therapies has been the subject of many trials, most of which are either too small to be conclusive or have a too brief follow-up. The rationale for combining the two modalities was the possibility of finding synergistic or additive effects on tumour cells. The two therapies have different spectrums of toxicity which makes their simultaneous use easy. A review of chemoendocrine trials in advanced disease showed an advantage in terms of remission rates in all of the studies compared to endocrine therapy alone. In about half of the published trials the comparison vs chemotherapy alone resulted in an increased remission rate. There was no advantage in terms of survival in either comparison, but the higher response rate for the combination justified its being tested in the adjuvant setting.

Factors involved in interpreting results related to this issue are illustrated by three trials. In the NSABP Trial B-09 779 patients were randomised to receive either PF (L-PAM and 5-fluorouracil) or the combination of the two cytotoxics with tamoxifen (PTF) [31]. The results show a qualitative difference of response according to age and steroid hormone receptor status (Table 4). While patients with ER+ and PR+ primaries in both age groups benefit from the adjuvant combination in terms of DFS, there is a tendency for the patients with one of the receptor types classified as negative who received chemoendocrine therapy to have a shorter DFS and OS, especially if premenopausal. One explanation for this derives from experiments showing a clear antagonism between tamoxifen and both L-PAM and 5-fluorouracil, in which the endocrine agent inhibits the cytotoxic efficacy of the two chemotherapeutic agents [32]. Based upon these experimental data, the results of the NSABP trial may be interpreted. In younger women, especially those with ER− tumours, for whom the degree of efficacy of chemotherapy is essential for control of disease, a reduced effect of the combination might be due to the antagonism between the cytotoxics and tamoxifen. In contrast, for patient subpopulations which are more responsive to tamoxifen therapy (postmenopausal age, receptor-positive tumours) the effect of the hormone therapy is sufficient to produce some benefit when compared with the chemotherapy, known to be less effective in these patients, at least within the first 5 years of follow-up. In fact, in trials with a direct comparison between the two treatments, tamoxifen and multi-agent chemotherapy, a significant advantage in favour of the cytotoxic regimen in the premenopausal cohort, and for the tamoxifen therapy in the postmenopausal women has been observed [33, 34].

Table 4. 5-year DFS rates and OS rates for patients included in NSABP Trial B-09 by menopausal and receptor status

Patient group	5-yr DFS (%)			5-yr OS (%)		
	PF	PFT	*P*	PF	PFT	*P*
All	47	52	0.002	67	67	0.8
Age <50	49	50	0.98	67	64	0.27
ER− PR−	41	38	0.4	56	44	0.06
ER− PR+	55	43	0.4	65	66	0.9
ER+ PR−	55	41	0.08	70	56	0.07
ER+ PR+	51	60	0.1	69	75	0.4
Age >49	44	54	0.001	67	70	0.27
ER− PR−	29	39	0.4	44	46	0.9
ER− PR+	45	48	0.9	58	59	0.7
ER+ PR−	52	48	0.6	75	67	0.3
ER+ PR+	45	56	0.002	76	74	0.9

PF = L-PAM + 5-fluorouracil, PFT = PF + tamoxifen.

In Trial III of the International Breast Cancer Study Group the combination of chemotherapy and tamoxifen (CMF combination with low-dose continuous prednisone, 7.5 mg a day, and tamoxifen: the CMFp+T regimen) administered for 12 courses was compared to p+T alone given for 12 months, and to a surgical control group [22]. Table 5 describes the 5- and 9-year results which indicate the late appearance of a significant OS advantage as compared to an early DFS benefit in favour of the patients who received the combined chemoendocrine therapy. The significant benefit for postmenopausal women treated with the combination in comparison with the surgical controls has also been indirectly confirmed in another large trial of the IBCSG (Trial V), in which postmenopausal women received either a short course of chemotherapy alone or a prolonged therapy comprising a 6-month course of the CMFp+T combination. The 5-year DFS rate for the single course was 35% as compared to 52% for the CMFp+T treated postmenopausal patients ($P = 0.0005$). The overall survival at 5 years' median follow-up was 65% and 75%, respectively ($P = 0.08$). The recently reported preliminary results of an Italian trial showed an improved control of disease, especially in postmenopausal women, by the combination as compared to both chemotherapy alone and tamoxifen alone in a patient population with N+ and ER+ disease [34]. The benefit from the combination was mainly evident in patients with a large number of positive nodes, i.e. with a more aggressive

*Table 5. 5-year and 9-year DFS rates and OS rates for postmenopausal patients 65 years old or younger included in Trial III of the IBCSG. Overall results and by oestrogen receptor status**

Patient group	DFS (%)		OS (%)	
	5-yr	9-yr	5-yr	9-yr
All				
Observation	30	19	59	38
pT	42*	31*	63	41 (*)
CMFpT	58*	41*	70	53 (*)
ER+				
Observation	30	23	72	45
pT	55	32	80	42
CMFpT	60	32	74	52
ER−				
Observation	30	21	45	33
pT	20*	17*	37	22*
CMFpT	63*	46*	63	57*
ER unknown				
Observation	30	17	56	35
pT	44 (*)	35 (*)	63	47
CMFpT	57 (*)	46 (*)	70	53

*Statistically significant difference between pT and CMFpT.
(*) $0.1 < P > 0.05$ for comparison between pT and CMFpT.
pT = prednisone and tamoxifen (see text for details of treatments).

presentation. Some evidence exists that prolonging the duration of treatment with tamoxifen beyond cessation of initial chemoendocrine therapy might provide additional benefit, especially if DFS is taken into consideration [35]. On the other hand, the issue of treatment of premenopausal patients with tamoxifen after cessation of therapy with either chemotherapy alone or with combined CMF and tamoxifen remains unsettled. A commentary on the different issues of the use of the drug in premenopausal women was recently published in regard to its use as a chemopreventive agent [36]. Effects of ovarian hyperstimulation in premenopausal patients on tamoxifen as well as patterns of relapse in young women after cessation of adjuvant tamoxifen treatment are matters of concern, and are the basis for the requirement for all premenopausal patients who receive long-term tamoxifen to be treated within the framework of clinical trials.

Results of the combination of chemotherapy and ablative surgery have been reported only from a single study, Trial II of the IBCSG [37]. This trial investigated the role of oophorectomy followed by 12 courses of chemotherapy in pre- and perimenopausal women with four or more positive axillary nodes. While the 4-year results did not differ for the two treatment groups, an analysis at 8 years' median follow-up showed some benefit in favour of the combined treatment which appeared only after 5 years. Although not statistically significant, the difference was confined to the subpopulation with ER+ tumours. Interesting also is the fact that averted relapses in the oophorectomy group were observed exclusively in the skeleton and also in patients with an aggressive presentation (i.e. those with 4 or more positive axillary nodes). In fact, it is known that bony metastases have a slow course. Other ongoing trials are currently investigating the same type of treatment.

PATIENTS WITH NODE-NEGATIVE DISEASE

This has been a matter of controversy in recent years. Patients with node-negative disease generally have a better prognosis and the absolute differences in outcome between those who received adjuvant therapy and those who did not are likely to be small, especially during the first 5–10 years after diagnosis. An attempt to identify factors to predict a higher relapse rate and a shorter survival and thus assist in the selection of a population which will have a larger benefit in terms of absolute response has been only partially successful. Patients with ER-negative primaries and with large tumours may be considered as having a somewhat worse prognosis, but their exclusion did not lead to the selection of a population which had, in the context of randomised trials, an estimated relapse rate at 5 years of less than 20%. Table 6 lists the trials carried out in populations without involved axillary nodes. A overall survival analysis of the data from these trials indicates no statistically significant survival differences, which is expected due to the relative short follow-up period in the majority of the studies. Another important observation is that the prognosis of the no adjuvant therapy cohorts is worse than expected. In the NSABP Trial B-14, 28% of the patients, all of whom had ER+ tumours, were estimated to relapse within five years. In IBCSG Trial V, in which patients entered before histopathological determination of prognostic factors (perioperative randomisation), 32% of the adjuvant untreated N− patients were estimated to relapse within 5 years.

The search for prognostic factors which might predict either a low-risk N− population or a high-risk cohort takes into account various histopathological, functional and biological features. Some prognostic relevance has been associated with the following features: tumour size (2 cm or larger vs smaller), site of the primary (internal quadrants of the breast vs other), nuclear and histological grade (poor and high, respectively, vs other grades), labelling index (high vs low), flow cytometry analyses (aneuploid or diploid with a large S-phase component vs diploid with a small S-phase fraction), oestrogen receptor content of the tumour (low concentrations or no detectable receptors vs high concentrations), expression of epithelial growth factor receptor (high vs low), amplification or overexpression of the c-*erb*-B2 oncogene (high vs low) and the expression of a lysosomal enzyme, cathepsin-D (high vs low). The prognostic value of each of these factors is under investigation, as is the benefit obtainable from adjuvant systemic therapy for the N− patient population. The effectiveness of adjuvant therapy has unequivocally been established by recent studies. The magnitude of the benefit is, however, small. Furthermore, it is unclear at present if a statistically significant overall survival advantage will appear. Until this question is clarified it is recommended that all patients be treated within the framework of clinical trials. Before treating such patients outside of clinical trials, risks of acute and potentially delayed toxicities, as well as issues of small magnitude of benefits to be derived, and lack of a clear overall survival advantage, must be explained before a mutual therapeutic decision is made.

DEFINITION OF BENEFIT TO PATIENTS IN TRIALS

Adjuvant systemic therapy does not provide cure for most of the treated patients. It is roughly estimated that it reduces relapse in one-third of the patients, which corresponds to a reduction in death rate of about one-fifth to one-sixth as compared with patients who do not received adjuvant therapy. This magnitude of effect is easily missed when results from individual randomised studies are analysed, even if 500–1000 patients were

Table 6. Trials of adjuvant systemic therapy in node-negative breast cancer. All trials evaluate chemotherapy with exception of NSABP trial B-14 in which tamoxifen is used

Trial [ref.]	Therapy	No. of patients/population	Year	DFS (%) Treated	DFS (%) Control
OSAKO [38]	LMF × 6	122/All	14	62	54
Midlands [39]	LMF × 8 low-dose	543/All	5	75	74
Mainz [40]	CMF × 12	175/All	5	82	72
Wien [41]	CFVbM × 8 (in 3 years)	128/All	5	86	78
Cardiff [42]	VAC × 6	52/ER−	3	83*	71*
Milan [43]	IV CMF × 12	90/ER−	7	85*	42*
NSABP B-13 [44]	M>F × 13	741/ER−	5	74*	65*
Intergroup [45]	CMFP × 6	406/ER− or ER + ifT>3 cm	5	83*	61*
Trial V [17]	IV CMF × 1 (periop.)	1275/All	5	74*	68*
NSABP B-14 [44]	TAM × 5 yr	2644/ER+	5	82*	72*

*Significant difference between treated and control.
L = chlorambucil, Vb = vinblastine, VAC = vincristine, dactinomycin and cyclophosphamide and P = prednisone.

included, because a yearly death rate of about 5% implies the capability to detect annual differences of less than 1% relative to the entire population.

The overview or meta-analysis of the results of trials which individually compared one therapy to another evaluates whether, in the presence of observed modest differences, the null-hypothesis (of no treatment effect) may or may not be rejected. The main advantage of summing up the results from all available trials into an overview relates to the possibility of detecting small but meaningful treatment effects otherwise of doubtful relevance. Furthermore, indirectly it increases the interest of physicians and communities in improving upon modest but real treatment effects. Among the disadvantages of an overview is the over-interpretation of the observed magnitude, and the tendency to perform indirect comparisons between therapies which were never or rarely directly compared (in a randomised trial) [47]. It should be concluded that the advantage of detecting small outcome differences may be considered the strength as well as the weakness of an overview, and thus analysis of individual trials must remain the basis for clinical and research purposes [48].

The most extensive overview included all available results from published and unpublished trials of almost 30 000 patients [49]. The trials compared tamoxifen with no adjuvant therapy, or tamoxifen plus a second treatment vs the second therapy alone (e.g. tamoxifen plus radiation therapy vs radiation therapy alone), and trials which compared chemotherapy with no adjuvant therapy or to chemotherapy plus a second therapy vs the second therapy alone (e.g. chemotherapy and tamoxifen vs tamoxifen alone). The estimated reduction of mortality within the first five years (most of the trials were in an early stage of follow-up) is described in Table 7. From the evidence of indirect comparisons, chemotherapy is the most effective treatment for younger women, while tamoxifen is the most effective therapy in postmenopausal patients. It is, however, clear from results of some trials that tamoxifen can also be very useful in some cohorts of premenopausal women, and that chemotherapy yields similar results in postmenopausal and premenopausal patients, considering a long enough follow-up. For a definitive solution of the controversy the issues must be studied in comparative trials.

Quality-of-life oriented evaluation

Analysis of results from clinical trials which investigated the relevance of adjuvant therapy for the treated populations focused upon benefits in terms of disease-free survival and overall survival. A recurring observation in individual trials is the relatively early appearance of a DFS benefit for treated patients and the occasional late emergence of an overall survival advantage. Another end point was developed which takes into account subjective toxicity and life with symptoms of disease allowing for comparisons. The end point is *T*ime spent *W*ithout *S*ymptoms of recurrent disease and *T*oxic effects of therapy, or TWiST [50, 51]. In the initial development of the analysis, an entire month of TWiST was removed for any month in which subjective side effects of therapy were recorded, even those which lasted a single day or less. Three months were removed beyond the end of adjuvant therapy to allow hair regrowth for patients with alopecia and adjustment for those with significant weight gain. The same time period was removed also in case of an isolated

Table 7. Reduction in the mortality rates for patients of adjuvant prolonged chemotherapy vs no adjuvant chemotherapy and adjuvant prolonged tamoxifen vs no adjuvant tamoxifen

Type of therapy	Typical reduction (%) in annual odds of death (S.D.) Age <50	Age ≥50	Any age
Tamoxifen	−1 (8)	20 (3)	16 (3)
Chemotherapy (CMF-type regimen)	26 (7)	8 (6)	17 (5)

Table 8. Components of Q-TWiST for the three treatments in trial III accumulated within 84 months of randomisation

	CMFp+T	p+T	Observation
TOX	9.6	2.0	0.0
TWiST	50.3	47.1	41.5
REL			20.9
Q-TWiST	7.1	12.9	
($u_{tox} = u_{rel} = 0.5$)	58.7	54.6	51.9

TOX = average months of experienced toxicity, REL = time with overt sysmptomatic relapse, Q-TWiST = calculated for arbitrary utility coefficient of 0.5 ($u_{tox} = u_{rel} = 0.5$) for both TOX and REL.

local recurrence. The remainder of a patient's lifetime was removed only if the patient developed distant metastases or a second malignant disease other than breast cancer. The method was initially applied to a trial (International Breast Cancer Study Group Trial III) [50], which investigated one year of chemoendocrine therapy (CMFp+T.) vs. one year of adjuvant endocrine therapy alone (p+T) vs an observation group. During the first years after adjuvant therapy patients in the observation group had a much larger TWiST than did the treated patients. However, as DFS benefits began to emerge and to increase for the patients who had adjuvant therapy, their TWiST increased to such an extent that after a 72-month period their average gain was 6 months compared to the average value for the observation patients. This advantage was statistically significant. This pragmatic approach, in which life with toxicity and life beyond relapse were compared to death, was then further modified to allow quality adjustments and extend the comparative methodology to include the individual patient's perceptions of the quality of her life with toxic effects and with relapse [51]. A quality-adjusted TWiST method (Q-TWiST) which better suits a quality of life-oriented approach, allowed the application of utility coefficients to every time-component spent with either toxic effects or with symptoms of disease, and to describe the ranges of values for which the average gain in terms of adjusted TWiST will indicate the significant superiority of one treatment over another. Table 8 describes the components of Q-TWiST for the three treatments in Trial III. Average months of experienced toxicity (TOX), time without symptoms and toxicity (TWiST), and time with overt symptomatic relapse (REL) accumulated within 84 months of randomisation, with Q-TWiST calculated for arbitrary utility coefficient of 0.5 for both TOX and REL are shown. In some of the ongoing trials, data are being collected from the patients on their perception of toxicity, symptoms of disease and well-being and, especially, their coping ability by time of diagnosis [52, 53], and it is likely that the quality of life considerations will increasingly be used for evaluating benefits from the therapies.

Chemotherapy regimens and toxicities

Many chemotherapy regimens were included in trials of adjuvant therapy for early breast cancer and some were subsequently widely used. The question of whether there are data to prove one regimen superior to the others can only partially be answered. The cyclophosphamide (C; 100 mg/m^2 orally, days 1–14), methotrexate (M; 40 mg/m^2 intravenously days 1 and 8), 5-fluorouracil (F; 600 mg/m^2 intravenously Days 1 and 8) combination, (CMF), given every 28 days has been found to be superior to single-agent therapy, mainly melphalan 0.15 mg/kg, daily for 5 consecutive days every 6 weeks, and in one large trial also cyclophosphamide 130 mg/m^2 daily for 14 days every 28 days. The acute toxicity of the CMF regimen includes gastrointestinal side-effects, mainly nausea, vomiting, some mucositis and diarrhoea, and in about 50% of the patients alopecia which requires the use of a wig by most. The use of more complex regimens including either prednisone alone at low-dose continuously or at high dose, intermittently, or prednisone and vincristine (the CMFVP regimen) administered continuously did not improve outcome in trials of direct comparison. To improve on therapeutic index by excluding cyclophosphamide and using chlorambucil (LMF regimen) has been attempted but the results of a single trial by the Swiss Group are not conclusive. Late side-effects of cytotoxic drug regimens were reported almost exclusively for melphalan combinations by the NSABP. There was an 11 fold increase in acute leukaemia and a 24 fold increase in acute myelogenous leukaemia within the first 10 years of follow-up after a 2 year treatment with this drug [54]. Analysis of second malignancies with CMF or LMF did not reveal differences between the treatment groups and the controls. The issue of doxorubicin-containing regimens has been discussed previously in this paper. Its use with cyclophosphamide or with melphalan plus 5-fluorouracil has been compared to the CMF combination in premenopausal women (or postmenopausal women defined as not responsive to tamoxifen). It was found to yield a similar outcome with less acute toxic effects due to a shorter treatment time with the anthracycline combination as compared to the CMF [19].

Breast conservation and adjuvant systemic therapies

Most of the trials regarding the use of adjuvant systemic therapies were carried out in patients who had undergone mastectomy. Adjuvant therapy was, therefore, usually started after a delay of 4–6 weeks. The increasing proportion of patients who choose a breast conserving procedure, which implies, in accord with our present knowledge, irradiation of the remaining breast, raises a question of priorities. Combined chemotherapy and radiation therapy has been reported by some as a feasible procedure, but others observed an impaired cosmetic result [55]. The use of both modalities in a sequential manner might be the best solution. Data are available showing that radiation may be delayed until after the systemic therapy has been completed (3–6 months after surgery), because the breast relapse rates for patients whose tumours were small enough for breast conserving therapy is below 1% within this time period. For adjuvant systemic therapy, the only data available are those which indicate a lack of negative consequences for start of therapy delayed 4–5 weeks as compared to the immediate delivery of treatment. Ongoing trials will provide some clear answers to the sequence and to the timing questions.

Treatment of elderly patients

Breast cancer in the elderly is a considerable public health problem. About 45% of all newly diagnosed breast cancers are estimated to occur in women above the age of 65. In this age group the yearly incidence rate of breast cancer is estimated to exceed 320 per 100 000 population [56, 57]. Until recently, most breast cancer clinical trials excluded elderly women, possibly because of concern that competing causes of death [58] in this population, especially in women with comorbid conditions and compromised functional status, might obscure true treatment effects. Although this is a valid argument against testing a new breast cancer treatment only in the elderly, there are good

Table 9. Trials of adjuvant systemic therapy in a population of elderly women

Trial and population	Therapies	No. of patients	Year reported	Results DFS (%) Treated	Control
ECOG 65–84 yr	TAM 20 mg × 2 yr	170	4	73	52*
Danish 70–79 yr	TAM 30 mg × 1 yr	509	6	41	39
Trial IV 66–80 yr	TAM 20 mg + p 7.5 mg × 1 yr	320	8	36	22*

*Significant difference ($P<0.01$, log rank test).

reasons with respect to cost/benefit to test new and potentially improved therapies in elderly patients. Another factor in such trials in the elderly is the fear of excess toxicity in this group, especially in trials which involve cytotoxic agents. Some investigators have dealt with this problem by arbitrarily reducing doses [59], while others have suggested that doses be based on creatinine clearance [60]. Another reason for the lack of breast cancer chemotherapy trials in the elderly is the general belief that chemotherapy is not effective in postmenopausal patients (roughly aged 50 to 65) and hence in those older than 65. However, in view of two chemotherapy trials in node-negative breast cancer [61, 62] which found a significant effect in postmenopausal women, it is now appropriate to consider chemotherapy trials in some subgroups of elderly patients. Table 9 summarises the results of the trials specifically carried out in an elderly population. Most adjuvant trials involved tamoxifen. The best result was obtained in the smallest study, in which a 2-year therapy schedule was used [63]. Intermediate results were obtained with combined tamoxifen and prednisone for only one year [64]. The statistically significant difference in disease-free survival (DFS) among the treated and the controls did not translate into a significant overall survival difference, although the reduction in odds of death for the ECOG and the International Breast Cancer Study Group (IBCSG) Trial IV were similar. The combination of radiation therapy and tamoxifen for the duration of one year did not change the course of the disease within the first 6 years, as compared with radiation therapy alone [65]. This might be because one year tamoxifen therapy reduces almost exclusively first relapses in local and regional relapses, which are also reduced by radiation therapy [66, 67]. The long-term effect of systemic therapy vs radiation treatment might differ, but this is likely to be evident only after several years, by which time the effects in the elderly population might be obscured by competing causes of death.

Present or planned trials in the elderly include one that randomises between tamoxifen and mastectomy followed by tamoxifen, and another between lumpectomy plus radiation therapy and lumpectomy plus tamoxifen. It is essential that clinical trials are conducted specifically in this age group which has such a high cancer incidence, and not to accept treatments for the elderly based exclusively on biases and on data from trials in younger patients as they are likely to hide aspects which are age-specific.

QUESTIONS FOR THE 1990s

Many questions have been incompletely answered during the years and yet maintained a potential importance for both patient-care considerations, and theoretical possibilities for improvement of outcome [68]. These include issues related to: (i) endocrine and chemoendocrine therapies; tamoxifen and ovarian ablation in premenopausal women; chemoendocrine therapies in pre and postmenopausal patients; tamoxifen in patients with ER-negative tumours; duration and dose of tamoxifen therapy; new anti-oestrogens or other hormonal agents (like aromatase inhibitors) with a different spectrum of endocrine activity. (ii) Intensive treatment (dose and schedule); with the aid of bone marrow reinfusion and of CSFs. (iii) New use of available drugs; alternating non-cross resistant combinations; sequencing of 5-fluorouracil and methotrexate; use of 5-fluorouracil and tetrahydrofolates; sequencing endocrine and chemotherapies. (iv) Biological response modifiers to change kinetics of tumour cells, among others TGF-alpha and TGF-beta; antibodies toward growth factors.

The last decade of the century is likely to provide us with some answers to questions related to the aetiology and physiopathology of breast cancer, but also to some therapeutic questions which might even have a more immediate impact upon our ability to care for the patients.

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What has Radiation Biology Contributed to the Evolution of Radiotherapy?

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BACKGROUND

TWENTY YEARS ago, most radiotherapists would usually have thought that the only way to improve results was to increase the dose to the tumour. This was right to some extent. This concept was, of course, limited by the normal tissue tolerance. However, it reflects why most efforts occurring between 1950 and 1970 were dominated by this approach. Hence, the clinical advances in developing the performance of linear accelerators, radiation physics dose calculations and brachytherapy techniques occupied the foreground of the theatre of clinical research while radiobiologists were obscurely working in the wings.

SUMMARY OF EMPIRICAL CLINICAL EXPERIENCE

The evidence of a dose-time relationship was clearly documented from clinical experiences in most solid tumours (head and neck, breast, gynaecological): radiotherapy was preventing the growth of subclinical aggregates of tumour cells in about 90% of the cases when doses of about 50 Gy were delivered in 5 weeks and 25 fractions. Increasing the dose to 70 Gy was usually sufficient to control 70–90% of tumours of less than 3 cm but the prediction of tumour response was increasingly difficult and the failure rates much higher when tumour volumes were beyond 5 cm diameter. It was then obvious that mathematical models based upon an even damage at each fraction up to the killing of the last tumour cell after a sufficient number of fractions was not fully representative of the response of most tumours to radiation. Hence, reasons for radiation resistance were investigated and gradually emerged from radiobiology and radiobiologically oriented clinical experiments.

RADIATION RESISTANCE

Does radiation resistance exist? Why, for an equal tumour volume, does radiation therapy fail in some tumours while controlling others? Very few human tumour cell lines can survive doses of 70–80 Gy delivered under optimal conditions. Intrinsic radiation resistance is a rare phenomenon (high grade glioblastoma for instance) and even in some "radiation resistant" tumours such as malignant melanomas, very large variations of radiation response are observed, including excellent responsiveness to doses consistent with normal tissue tolerance.

Then, in most situations, the so-called "resistance to radiation" will in fact be resulting from (1) Geographical misses: either by an insufficient coverage or by ignoring the actual tumour spread (macroscopic or microscopic); (2) impossibility to deliver the required dose to the tumour without serious damage to vital normal stuctures (such as lung, heart, spinal cord, bowel, kidney); (3) radiobiological factors reducing the therapeutic gradient between normal tissues and tumours such as hypoxia and cell kinetics.

Several options are offered in modern radiotherapy to fight against each of these three major causes of failures. This paper will only concentrate on the radiobiological factors of radiation resistance.

THE OXYGEN EFFECT

Hypoxia has been known as a cause of radioresistance since 1935 [1] and was later documented in the laboratory by Gray [2] and Lacassagne [3]: most tissues irradiated in the absence of oxygen are 2.5 to 3 times more resistant than in the presence of oxygen at a normal pressure. A number of applications of this phenomenon has led to experimental work both in the laboratory and in clinical research:

- Irradiation under hyperbaric oxygen pressure (HBO).
- Irradiation using beams of a lesser oxygen dependence such as neutron beams.
- The use of oxygen mimetic radiosensitisers and bioreductive agents.

Radiotherapy and hyperbaric oxygen

Nearly all randomised trials have shown a significant improvement of local control in patients treated under hyperbaric oxygen (at an oxygen pressure of 2.5 to 3 atmospheres) as compared to

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