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Surgery plus Adjuvant Chemotherapy — A Review of Therapeutic Implications

I. Breast Cancer

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Surgical adjuvant trials now constitute a major aspect of ongoing clinical research. There has been a waxing and waning of therapeutic enthusiasm for the concept of combining drug treatment with surgical local control therapy. In the late 1950s and early 1960s there was enthusiasm for short-course adjuvant treatment to eradicate circulating tumor cells. The failure of most of these studies to significantly improve survival led to disillusionment with the approach. In the early 1970s the concept had a rebirth, with prolonged drug treatment regimens being utilized to eradicate microscopic metastatic foci. Early results indicated a positive effect in breast cancer and osteosarcoma and an explosion of enthusiasm resulted. As longer follow-up diminished the early positivity of some studies a backlash developed against the approach. There is now a mood of cautious optimism about progress being made, but there is also a clear realization that adjuvant chemotherapy is not a panacea and that the analysis of adjuvant trials will be a long-term proposition.

It is the purpose of this paper to review the current status of adjuvant trials in breast cancer with emphasis on the experimental designs utilized and the end-points for analysis available. This review will not attempt to be encyclopedic and touch on every trial ever reported. It will limit itself to a majority of available reports covering the entire range of design approaches. Future reviews in coming issues will cover colorectal cancer and osteosarcoma.

A successful combined modality approach in breast cancer has two essential components, an effective approach to local control and an equally important approach to effective metastatic control. There is a tendency to compartmentalize these two approaches, and medical oncologists tend to view the surgery in surgical adjuvant trials as a generic homogeneous given. Most adjuvant protocols, when examined, give little information on the surgical procedure and just list the procedures that are acceptable for study eligibility. Many protocols allow a heterogeneity of surgical procedures and some in addition allow postoperative irradiation at the discretion of the referring physicians.

Two views can be given to this heterogeneity in local control approaches allowed in many adjuvant trials. One view is that local control therapy is minimally important as regards ultimate metastatic failure. Since metastasis occurs prior to diagnosis, only an effective disseminated modality will improve the final results. Therefore the heterogeneity in local control techniques in adjuvant trials is acceptable. A second view would hold that at least for some patients, effective local control can diminish metastatic spread. In addition, for others effective local control can maximally diminish the residual tumor cell burden so as to give adjunctive drug treatment an optimal chance to achieve total cell eradication. Therefore heterogeneity in local control techniques in adjuvant trials should be minimized. At this moment definitive data to support either view are lacking. Minimizing the variables outside of the therapies under test is a sine qua non of good experimental design, and therefore it would be safer to adhere to the second view until it is disproven by data.

The final evaluation of an adjuvant trial will take many years of follow-up. The critical question that requires answering for the practicing oncologist is whether

Table 1. Critical elements required to determine the definitive value of a chemotherapy regimen as a surgical adjuvant in primary breast cancer

I.	An adequate control of experience with surgery only
II.	Adequate follow-up time for relapse-free survival, overall survival, and toxic cost – minimum 5 years
III.	Adequate numbers for critical subsets A) Pre. vs postmenopausal B) Axillary node-negative vs -positive (1–3+ vs ≥ 4+) C) Clinical stage I vs stage II vs stage III D) ER+ vs ER– (modern trials)

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any adjuvant regimen can be definitively recommended as routine treatment in oncologic practice. The answer to the question concerning the definitive value of a given regimen will require three critical elements (Table 1). The first will be an adequate control of an experience with surgery only. As this paper will attempt to show, a variety of controls exist and at this time one can have opinions but not certainty as to which types are acceptable and/or the best. The second component is an adequate follow-up time for relapse-free and overall survival. It is well recognized that relapses continually occur in breast cancer patients and that 5-year survival is not a guarantee of cure for this disease. On the other hand it is a reasonable benchmark, as the great majority of relapses in women with or without positive axillary nodes will have occurred by 5 years after treatment. What remains to be determined is when actuarial projections of 5-year survival data can be viewed with confidence. It will be important to view what the projections of 5-year survival were when 10% of patients in a trial were actually followed by 5 years and compare that to the data when 25%, 50%, 75%, and ultimately 100% had passed that critical period. An extreme view would be that you cannot know what will happen at 5 years until it happens.

The third element will be adequate numbers of patients in critical subsets. The heterogeneity that exists within the disease called breast cancer is now well established. Comparing results for treatment versus control as a totality is no longer acceptable. It is essential to separate out axillary node-negative from node-positive patients, premenopausal from postmenopausal, and estrogen receptor-positive from estrogen receptor-negative when available. This makes for eight critical subsets. If you add degree of axillary nodal involvement (1–3+ vs > 4+) and tumor size (T_1 vs T_2 vs T_3) the critical subsets jump to 48. A regimen of value only for premenopausal women with 1–3+ nodes who are estrogen receptor-positive could well be lost if only a total mass of patients were analyzed. This requirement for analysis within critical subsets means that only a few single institutions can undertake studies and hope to attain adequate numbers. The great predominance of studies will require collaboration of multiple institutions. This will therefore require group discipline and stringent quality control to minimize the compromise and dilution phenomena.

Only a few adjuvant trials meet the above criteria. It should not be forgotten that most of the studies reported in journals, and in published symposia on adjuvant treatment, are in a preliminary stage of interim analysis. They contain actuarial projections of 2- to 3-year relapse-free survival, with many patients being under follow-up for less than that period and some still under active treatment.

Adjuvant trials in breast cancer can be broken down into three basic categories as follows:

I) Prospective randomized trials with surgery-only control group

A. Prior to 1970 – single and multiple courses (Table 2).

B. Post 1970 – prolonged chemotherapy (Table 3).

II) Prospective randomized trials without a surgery-only control

A. With L-PAM control (Table 4).

B. With CMF control (Table 5).

C. With other chemotherapy 'controls' (Table 6).

III) Historically controlled trials (Table 7).

Each of these categories will be looked at separately and in the discussion the therapeutic implications will be analyzed. The regimens under evaluation can be divided into four categories and are shown in Table 8, which does not include regimens from Group I A above (randomized trials prior to 1970). The actual details of some of the modern chemotherapy regimens utilized are detailed in Table 9.

The trials prior to 1970 in Table 2 meet some of the important criteria for definitive analysis. For the most part, they were prospectively randomized with a surgery-only control group and they all have adequate follow-up duration. What they lack are adequate numbers within meaningful prognostic subsets. The total numbers entered in some studies are quite large, but all include both axillary node-positive and -negative patients. By the time menopausal status and degree of nodal positivity are analyzed the numbers become quite small. Despite this, some evi-

Table 2. Breast cancer adjuvant: Prospectively randomized trials with a surgery-only control group prior to 1970

Group or investigator	Axillary nodes	Regimens	Number of patients
NSABP [14]	+ and –	1) Surgery 2) S + thio-Tepa one cycle	406 414
Nissen-Meyer [24]	+ and –	1) Surgery ± radiation ± castration 2) Above + cytoxan one 6-day course	554 534
NSABP [12]	+ and –	1) Surgery 2) S + 5-FU (one cycle)	207 450
Donegan [11, 19]	+ and –	1) Surgery 2) S + thio-Tepa postop. daily × 3 then weekly × 1 year	92 125
Mrazek [23]	+ and –	1) Surgery 2) S + nitrogen mustard postop. daily × 3 the every 3 months × 4	78 78

Table 3. Breast cancer adjuvant: Prospectively randomized trials with a surgery-only control group post 1970

Group or investigator	Nodal status	Regimens	No. of patients	Follow-up
NSABP [14–16]	+	1) Surgery 2) S + L-PAM (18 mo.)	169 179	5 years
NCI Milan [3–6]	+	1) Surgery 2) Surgery + CMF (12 cycles)	179 207	5 years
Osako [29]	+ and –	1) Surgery 2) Surgery + LMF Chlorambucil MTX 5-FU Prednisone } 6 mo. then BCG 18 mo.	124 118	3 years
Guys Hospital	+	1) Surgery 2) Surgery + L-PAM (24 mo.)	240+	~ 3 years
Manchester [10]	+	1) Surgery 2) Surgery + L-PAM (24 mo.) 3) Surgery + CMF (1 year)	130+	~ 3 years
Multicenter Breast Cancer Chemotherapy Group [34]	+	1) Surgery 2) Surgery + Cytotoxan Vincristine Methotrexate 5-FU	127 125	3 years
ECOG (Postmenopausal only)	+	1) Surgery 2) Surgery + CMFP 3) Surgery + CMFP + tamoxifen	–	Too early
ECOG (Postmenopausal < 65 years)	+	1) Surgery 2) Surgery + CMFP + tamoxifen	–	Too early

Table 4. Breast cancer adjuvant: Prospectively randomized trials with L-PAM as the control

Group or investigator	Axillary nodal status	Menopausal status	Regimens	Number of patients	Follow-up
NSABP	+	Pre + post	1) L-PAM 2) L-PAM + 5-FU	Total 741	2½ years
SWOG [17]	+	Pre + post	1) L-PAM 2) CMFVP	231 349	2 years
Mayo Clinic [1]	+	Pre + post	1) L-PAM 2) CFP 3) Irradiation + CFP	51 58 57	3 years

Table 5. Breast cancer adjuvant: Prospectively randomized trials with CMF as the control

Investigator	Axillary nodal status	Menopausal status	Regimens	Number of patients	Follow-up
NCI, Milan [31]	+	Pre	1) CMF (12 cycles) 2) CMF (6 cycles)	160 165 coded	3 years
CALGB	+	Pre + post	1) CMF 2) CMFVP 3) CMF + MER	135 and 144 144	1½ years
Case-Western [18]	+	Pre + post	1) CMF 2) CMF + tamoxifen 3) CMF + tamoxifen + BCG	–	2–3 years
UCLA	+	Pre + post	1) CMF 2) CMF + BCG 3) CMF + BCG + tumor vaccine	–	> 3 years
ECOG	+	Pre	1) CMF 2) CMFP 3) CMFP + tamoxifen	–	Too early

Table 6. Breast cancer adjuvant: Prospectively randomized trials with a nonestablished control group

Investigator	Axillary nodal status	Menopausal status	Regimens	Number of patients	Follow-up
NSABP	+	Pre + post	1) L-PAM + 5-FU 2) L-PAM + 5-FU + MTX	Total 737	~ 2 years
NSABP	+	Pre + post	1) L-PAM + 5-FU 2) L-PAM + 5-FU + tamoxifen	Total 775	Too early
NSABP	+	Pre + post	1) L-PAM + 5-FU 2) L-PAM + 5-FU + *C. parvum*	Still ongoing	Too early
NCI, Milan	+	Post	1) CMF (6 cycles) then adriamycin + vincristine (4 cycles) 2) Same as above with escalating doses	Still ongoing	< 2 years

Table 7. Breast cancer adjuvant: Non-randomized trials

Group or investigator	Axillary nodal status	Menopausal status	Regimens	Number of patients	Follow-up
MD Anderson [7, 8]	+	Pre + post	1) FAC-BCG 2) Historical control	222 151	3 years
Univ. of Arizona	+ and –	Pre + post	Adriamycin + cytoxan A) node neg. 3 cycles B) node pos. 8 cycles	248	2–3 years
Univ. of Indiana [35]	+	Pre + post	1) Adriamycin + BCG 2) Adriamycin + cytoxan + BCG 3) Adriamycin + cytoxan followed by CMF	17 57 46	3 years
Cooper [31]	+	Pre + post	CMFVP	100	5 years

Table 8. Selected list of combinations in adjuvant trials

I.	*Non-adriamycin-containing*	Group
	1. L-PAM	NSABP
	2. L-PAM + 5-FU (PF)	NSABP
	3. L-PAM + 5-FU + MTX (PMF)	NSABP
	4. Cytoxan + 5-FU + MTX (CMF)	Various
	5. Chlorambucil + 5-FU + MTX ± prednisone (LMF)	Osako
	6. Cytoxan + 5-FU prednisone (CFP)	Mayo Clinic
	7. Cytoxan + 5-FU MTX + prednisone (CMFP)	ECOG
	8. Cytoxan + 5-FU MTX + vincristine (CMFV)	COG
	9. Cytoxan + 5-FU MTX + vincristine + prednisone (CMFVP)	SWOG, CALGB, Cooper
II.	*Adriamycin-containing combinations*	
	1. Adriamycin + cytoxan (AC)	Univ. Arizona Sydney Farber Cancer Institute
	2. Adriamycin + cytoxan + 5-FU (FAC)	MD Anderson
	3. CMF (6 cycles) and adriamycin + vincristine (4 cycles)	NCI, Milan
III.	*Hormone-containing combinations*	
	1. CMF + tamoxifen (CMFT)	Case-Western
	2. CMF + prednisone + tamoxifen	ECOG
	3. Tamoxifen	ECOG
	4. L-PAM + 5-FU + tamoxifen	NSABP
IV.	*Immunotherapy containing*	
	1. CMF + BCG	UCLA
	2. CMF + BCG + tumor cells	UCLA
	3. CMF + tamoxifen + BCG	Case-Western
	4. LMF + BCG	Osako
	5. FAC + BCG	MD Anderson
	6. L-PAM + 5-FU + *C. parvum*	NSABP

Table 9. Examples of drug regimens utilized as adjuvant therapy after mastectomy

Acronym	Drugs	Dosage and route	Days of administration	Recycle on day	Duration
1. L-PAM	L-PAM	6 mg/m² PO	1 to 5	43	2 years
2. PF	L-PAM + 5-FU 300 mg/m²	4 mg/m² PO	1 to 5	43	2 years
3. PMF	L-PAM	4 mg/m² PO	1 to 5	43	2 years
	Fluorouracil	300 mg/m² IV	1 to 5		2 years
	Methotrexate	25 mg/m² IV	1 and 5		
4. CMF	Cyclophosphamide	100 mg/m² PO	1 to 14		
	Methotrexate	40 mg/m² IV	1 and 8	29	1 year
	Fluorouracil	600 mg/m² IV	1 and 8		
5. LMF	Chlorambucil	4 mg/m² PO	1 to 14		
	Methotrexate	5–7.5 mg PO	1 to 3	29	6 months
	Fluorouracil	500–750 m PO	1 and 8		
6. CFP	Cyclophosphamide	150 mg/m² IV	1 to 5		
	Fluorouracil	300 mg/m² IV	1 to 5	43	10 cycles
	Prednisone	30 mg PO	1 to 7		
7. CVFM	Cyclophosphamide	300 mg IV	1 and 8		
	Vincristine	0.65 mg IV	1 and 8		
	Fluorouracil	500 mg IV	1	29	6 months
	Methotrexate	37.5 mg IV	8		
8. CMFVP	Cyclophosphamide	60 mg/m² PO	daily		1 year
(SWOG)	Fluorouracil	300 mg/m² IV	weekly		1 year
	Methotrexate	15 mg/m² IV	weekly		1 year
	Vincristine	0.625 mg/m² IV	weekly		10 weeks
	Prednisone	30 mg/m² PO	daily		1–14, 15–28, 29–42,
9. AC	Adriamycin	30 mg/m² IV	1	22	3–8 cycles
	Cyclophosphamide	150 mg/m² PO	3 to 6		
10. FAC	Fluorouracil	400 mg/m² IV	1 and 8		
	Adriamycin	40 mg/m² IV	1	29	2 years
	Cyclophosphamide	400 mg/m² IV	1		

[a] After a total dose of 300 mg adriamycin/m² change to CMF (cyclophosphamide 500 mg/m² PO day 2, methotrexate 30 mg/m² PO days 1 and 8; fluorouracil 500 mg/m² PO days 1 and 8)

dence of positivity exists in the available data for analysis.

The NSABP thio-Tepa trial was performed in two phases. The first phase was between April 1958 and October 1961. After Halsted radical mastectomy randomization was between placebo and thio-Tepa. For the first 104 patients 0.4 mg/kg IV was given at the time of operation, followed by 0.2 mg/kg IV on postoperative days 1 and 2. After this the operative day dose was reduced to 0.2 mg/kg ~ for the next 55 cases. Phase II ranged from October 1961 and May 1967 and included randomization among placebo, thio-Tepa, radiotherapy, 5-FU and oophorectomy.

Overall there was no benefit that could be observed in the thio-Tepa group. When subsets were analyzed no benefit could be discerned in patients with negative nodes, regardless of menopausal status. The same was true of postmenopausal patients regardless of nodal status. A positive effect was observed in premenopausal women with four or more positive axillary nodes. The median time to recurrence was 13 months in the placebo group and 45 months after thio-Tepa. The relapse-free survival and overall survival at 5 years are shown in Table 10.

Table 10. Five- and ten-year survival data for NSABP thio-Tepa trial [1]

Time	Relapse-free survival				Overall survival			
	Thio-Tepa		control		Thio-Tepa		control	
	(No.)	%	(No.)	%	(No.)	%	(No.)	%
5 years	(23)	34.8	(36)	13.9	(23)	56.5	(37)	24.3
10 years	(22)	31.8	(36)	11.1	(23)	34.8	(37)	13.5

The NSABP trial of 5-FU was part of the phase II aspect of the thio-Tepa trial described previously. The 5-FU dose was 15 mg/kg given on days 7, 8, 9, and 10 after surgery. The overall result was negative with no positivity observed in any subsets.

The trial reported Donegan lasted 10 years and closed in 1972. Randomization was performed by selecting alternate patients from a table of odd and even numbers. Following a standard radical mastectomy the treated group received 0.4 mg thio-Tepa/kg in the operating room, and 0.2 mg/kg on postoperative days 1 and 2. After discharge from the hospital the patients were to receive 0.2

mg/kg/week IV for 1 year, but the average duration of treatment was reported to be 7.2 months. A total of 217 patients were entered, with 125 assigned to adjuvant drug and 92 to the control group. There were 51 patients excluded for protocol violations, leaving 90 in the treated group and 76 in the control group.

The early data showed a recurrence rate at 2 years of 52.9% in the control group and 20.7% in the thio-Tepa group. Further follow-up, however, failed to demonstrate any benefit for the adjuvant group. It is of interest that local treatment failure was less frequent in the treated group (16% vs 48.3%) ($P > 0.05$).

The evaluation of nitrogen mustard (HN_2) by Mrazek et al. involved 156 women evaluated between 1956 and 1964. All patients received a Halsted radical mastectomy and then were randomly allocated to observation or HN_2 0.2 mg/kg at operation and 0.1 mg/kg on the first and second postoperative days. Similar courses were administered every 3 months 'to bone marrow tolerance' for a mean of 2.9 courses per patient.

There were recurrences in 50% of the control patients and 39.7% of the treated patients. Among postmenopausal patients there were 24/49 (48.9%) recurrences in the control group and 23/50 (46.0%) in the treated group. Among premenopausal patients there were 15/29 (51.7%) recurrences in the control group, as against 8/28 (28.5%) in the treated group. In node-positive patients the HN_2 group's recurrence rate was 25/43 (58.1%) while the recurrence rate was 74.3% (29/39) in the controls. For node-negative women it was 25.6% (10/39) in the control group and 6/35 (17%) in the HN_2 group. In premenopausal women with negative nodes no recurrences were observed in 14 women treated with HN_2 as against 4/14 in the controls (28.5%).

One of the studies with the longest follow-up is that of the Scandinavian adjuvant chemotherapy group chaired by Nissen-Meyer of Norway. Eleven hospitals in Finland, Norway, and Sweden entered patients between January 1965 and September 1975. The chemotherapy used was cyclophosphamide 5 mg/kg daily for 6 days beginning immediately after mastectomy, except in one hospital where it took place 2–4 weeks after surgery. The study includes 557 controls and 559 treated patients. With 12 years of follow-up recurrences have occurred in 232 of the treated and 284 of the controls. Death has occurred in 210 of the treated and in 265 of the controls. Both differences are statistically significant ($P < 0.01$). In addition to surgery all patients received postoperative irradiation, and 112 premenopausal women received prophylactic castration. The relapse-free survival and overall survival advantage for adjuvant drug is the same for this group as it is for the 660 postmenopausal women and 254 premenopausal women with intact ovaries.

Interpretation of the Nissen-Meyer study is complicated by the heterogeneity in the patient material and in the approaches to local control. In terms of initial control therapy there were 12 possibilities in the trial. This is derived from three surgical procedures and the variations of postoperative irradiation (yes or no) and prophylactic castration (yes or no). In terms of the patient material there were both axillary node-negative and -positive women, with all of the other potential subsets. While the total numbers seem large the numbers with positive nodes are not significantly greater than those found in the NSABP or Milan studies. There were only 416 node-positive women (~ 40% of total) broken down into 198 treated and 218 control. In this subset relapse-free survival showed a 10.73% advantage for drug at 7 years with a standard error of 5.40. In terms of overall survival the difference was not significant at only 1.83%.

The trials involving prospectively randomized comparisons of adjuvant drug with surgery only started in the 1970s (Table 3) and are the ones that have generated the most excitement and controversy. They all involve long-term usage of aggressive chemotherapy, which for the most part is combination chemotherapy.

In 1972 the National Cancer Institute launched a large-scale controlled trial of the use of chemotherapy as an adjuvant to surgical operation in women in whom cancer had already spread. This study was carried out by the National Surgical Adjuvant Breast Project (NSABP) headed by Dr. Bernard Fisher. Half the women were given L-phenylalanine mustard (L-PAM) after radical mastectomy and half were given a placebo. At the time of initial report in the literature treatment failures had occurred in 22% of 108 patients receiving placebo and 9.3% of 103 women given L-phenylalanine mustard [14]. This difference even then was only statistically significant at the 0.05 level for premenopausal women. Continued follow-up still shows no meaningful difference favoring adjuvant drug for women who are postmenopausal.

A follow-up of the NSABP data [15] has shown that at 48 months of follow-up the percentage of treatment failures overall is 48% in 169 placebo and 40% in 179 L-PAM patients, the P-value being 0.02. When the data are looked at broken down by menopausal status the data are as follows:

Age		Number of patients	% Treatment failure	P-value
≤ 49	Placebo:	60	55.0	0.005
	L-PAM	59	34.0	
≥	Placebo:	109	45.0	0.29
	L-PAM	120	43.0	

The only situation in which the L-PAM is statistically significantly superior to placebo is with premenopausal patients with 1–3 positive nodes, where the failure rate is

44% with placebo in 31 patients as against 13% with L-PAM in 32 patients at 4 years. The *P*-value is 0.005.

The first CMF adjuvant study was initiated on June 1, 1973. Patients with primary tumors staged as T_{1B}–T_{2B} or T_4 by the UICC TNM international classification were not considered eligible for inclusion in the protocol. Also excluded were those with N_2 or N_3 lesions, which meant either nodes fixed to one another or to other structures or supraclavicular; infraclavicular nodes or edema of the arm. After mastectomy randomization was to CMF begun within 4 weeks of surgery or to no further treatment.

As of February 1, 1979 [5], the clinical benefit in terms of relapse-free survival of adjuvant CMF overall in 207 CMF-treated women as against the 179 controls remains highly significant ($P = 0.0001$) (Table 11). This benefit is seen exclusively in premenopausal women.

The CMF data are clearly positive in premenopausal women but do not indicate much benefit of this therapy in postmenopausal patients. When the L-PAM data and the CMF data are put together with earlier single-course thio-Tepa data of the NSABP an enigma is seen. All are negative in postmenopausal women and a dichotomy exists in premenopausal women. A single course of thio-Tepa is of value for the subset with ≥ 4+ nodes but not for the better-risk group of 1–3+ nodes. The more aggressive 18 months of L-PAM is of value for the 1–3+ nodes but not for the ≥ 4+ nodes. CMF is effective for both subsets. Since CMF is more effective in advanced disease this is encouraging for advanced disease, activity being predictive for adjuvant effect.

In Switzerland adjuvant chemotherapy is being evaluated in both node-positive and node-negative women with T1–3a lesions without evidence of metastasis. Between 1974 and 1977 a total of 254 women were entered into a protocol comparing modified radical mastectomy alone or the same plus adjuvant chemoimmunotherapy. The adjuvant chemotherapy involves six cycles of chlorambucil 6–8 mg/d1–14; methotrexate 5–7.5 mg d1–3, 8–10; and 5-FU 500–750 mg d1–8, all administered orally, plus prednisone 50 mg/d × 14 during the first cycle and 10 mg/d × 14 during the subsequent five cycles. After a certain period of the prednisone was dropped from the study due to toxicity. After the 6 months of drugs BCG was given every 4 weeks for 18 months.

The median observation time in this study is 34 months, with a range of 14–58 months. There is a clear-cut and highly significantly lower recurrent rate among node-negative patients receiving adjuvant therapy (6.9% vs 26.8%, $P = 0.007$) (Table 12) on the other hand, no significant difference exists in the node-positive group.

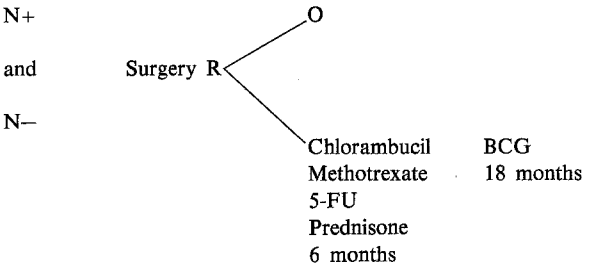
In Britain the Multicentre Breast Cancer Chemotherapy Group (MBCCG) began an adjuvant trial in 1975 involving women with T_{1-2}, N_{1a-b}, M_0 lesion. Primary treatment was not standardized and included simple mastectomy with or without deliberate axillary node sampling with postoperative radiotherapy, or modified radical mastectomy with or without irradiation. Randomization was to receive or not receive drugs after initial primary therapy. The chemotherapy involved cycles of cyclophosphamide, vincristine, and 5-FU on day 1, and 4–6 days later cyclophosphamide, vincristine, and methotrexate. Six cycles were given for approximately 6 months of treatment.

After 36 months recurrences have occurred in 56 of 127 controls as against 37 of 125 with adjuvant drug treatment. According to life-table analysis the recurrence

Table 11. Four-year relapse-free survival (%). In CMF adjuvant study as of February 1, 1979 [5]

Status	Control	CMF	*P*-value
All patients	47.3	63.1	0.0001
1 node +	58.0	76.7	0.02
2–3 nodes +	47.3	67.1	0.01
≥ 4 nodes +	35.2	44.8	0.03
Premenopausal			
All patients	43.4	70.0	0.00002
1 node +	52.2	80.9	0.01
2–3 nodes +	49.3	84.2	0.0005
≥ 4 nodes +	26.7	45.4	0.005
Postmenopausal			
All patients	51.7	56.5	0.22
1 node +	63.2	72.0	0.24
2–3 nodes +	45.4	53.0	0.10
≥ 4 nodes +	43.6	46.2	0.23

Table 12. Swiss breast cancer adjuvant study[a]. Data of Senn et al. [29]



Nodal status	Control		Treated	
	No. of patients	% Relapse	No. of patients	% Relapse
Negative	58	26.8	67	6.9 $P = 0.007$
Positive	60	47.4	57	30.0 $P = 0.425$

[a] Median follow up 34 months; range 14–60 months

rate at 3 years is 56% in the control group and 37% in the treated group ($P < 0.01$). When menopausal status in subsetted the 12-month relapse-free survivals for the controls are 70.3% and 76.4% in the pre- and postmenopausal women, respectively. In the adjuvant group it is 81.5% and 91.8%. The benefit for postmenopausal women at 1 year is statistically significant. In terms of overall survival no differences exist between treated controls, as only six patients have expired to date, indicating the preliminary nature of the study.

Three trials have been undertaken in which L-PAM is being used as a control (Table 4). All were started at a time when the preliminary analysis of the NSABP study indicated that this would be a highly positive study. With the clarity of longer follow-up L-PAM appears to be a poor control for postmenopausal women and even for premenopausal women with ≥ 4 positive axillary nodes. This will make interpretation of these trials more difficult.

The NSABP study immediately following the L-PAM trial compared L-PAM alone with L-PAM + 5-fluorouracil with an identical design. This trial has closed with nearly 750 patients having been entered. With a follow-up time in excess of 2 years for some patients, the preliminary data do not favor the combination in the premenopausal patients. On the other hand some advantage, in terms of relapse-free survival, is being observed for the combination in postmenopausal women with four or more positive nodes. This study has not been published in any detail and so full analysis will have to wait for longer, and more appropriate, follow-up.

In the Southwest Oncology Group Study CMFVP is compared with L-PAM. In this study women with positive nodes after modified or radical mastectomy were eligible. Stratification was according to menopausal status, number of involved axillary nodes (1–3 or > 4), and whether postoperative radiation was going to be administered or not. Patients were randomized to receive 2 years of L-PAM or 1 year of CMFVP. Treatment was begun 2–6 weeks after operation. Between January 1975 and February 1978, a total of 434 women were randomized. After February 1978 an additional 146 women were given CMFVP when preliminary analysis indicated superiority for the combination.

At the time of the most recent report 334 women had been analyzed, with a median follow-up time of 26 months. The overall recurrence rate is 33.1% for L-PAM and 15.4% for CMFVP ($P < 0.003$). The superiority for the combination, in terms of recurrence rate, is also highly significant for all premenopausal (32% vs 12.5%), and postmenopausal women (34% vs 17.3%) and for all women with 1–3 involved nodes (18.4% vs 5.8%) and ≥ 4 involved nodes (43.2% vs 22.6%). Overall survival is not significantly different between the two groups.

The Mayo Clinic has studied three regimens in 172 patients found to have either axillary node involvement or skin infiltration with ulceration or involvement of pectoral muscle or fascia. The surgery was either radical or modified radical mastectomy. The patients were stratified according to the size of their tumor (< 3.0 cm or 3.0 cm), the presence or absence of unfavorable local signs, extent of nodal involvement (1–3 or $\geq 4+$), and menopausal status. The patients were randomized to be treated with L-PAM, CFP, or CFP after postoperative irradiation. The analysis indicates that in terms of relapse-free survival projected out to 3 years, CFP with or without irradiation was superior to L-PAM. This superiority was exclusively observed in premenopausal women, no difference between any of the regimens being seen in postmenopausal women. In actual percentages of recurrences, in premenopausal women the L-PAM group had 8/19 (42%) as against 3/20 (15%) with CFP and 3/23 (13%) with CFP plus radiation.

A larger number of trials have been undertaken with CMF, as reported by the Milan group, used as a control (Table 5). This is a highly appropriate control for premenopausal women but is of dubious value for postmenopausal women, as seen from the latest data on the original Milan trial.

The second CMF adjuvant program was initiated on September 12, 1975. In this study women were randomized to receive either 12 or 6 cycles of CMF within 2–4 weeks from radical mastectomy. Postmenopausal women were withdrawn after the analysis of the first CMF study revealed a lack of meaningful effect for the regimen in this subset. The trial was continued only in premenopausal patients and was closed on May 31, 1978. With analysis allowing actuarial projection of relapse-free survival out till 3 years no difference between 6 and 12 cycles of CMF in premenopausal women has been seen [31] (Table 13).

CMF is the control in the ongoing study of cancer and leukemia group B. This trial involves women with operable breast cancer (Stage I, II, IIIA) with involved axillary nodes. Patients were stratified by age (< 50, $\geq$ 50 years), primary tumor size (< 3 vs > 3 cm), and whether or not they received postoperative radiotherapy.

Table 13. CMF: Six vs twelve cycles as adjuvant in premenopausal women with breast cancer. Data of Tancini and Bonadonna [31] $T_{1-3}N_1M_0$

	CMF 12 cycles	CMF 6 cycles
Number of patients	160	165
% Amenorrhea	79.3	84.4
% NED at 36 months	85.1	81.1
1–3 +	92.4	87.5
≥ 4 +	77.0	71.3
% Alive at 36 months	93.3	93.8

Randomization was to CMF, CMFVP, and CMF + MER immunotherapy.

At present 423 of these women are evaluable, with a median follow-up time of 17 months. There is no firm statistical evidence favoring any of the three regimens at the moment. There is no difference in relapse rates by menopausal status.

A trial comparing CMF alone with the addition of antiestrogen therapy and immunotherapy has been undertaken by Hubay et al. from Case-Western Reserve University. This trial was initiated in 1974 as a prospective randomized trial of CMF, CMF plus tamoxifen (CMFT) and CMFT plus immunotherapy with BCG, as adjuvant therapy in women undergoing mastectomy with involved axillary lymph nodes. This study is of particular interest because stratification was made by estrogen receptor assay for each of the three treatment groups.

A preliminary analysis at 36 months after mastectomy (Table 14) indicates that the estrogen receptor-negative (ER−) tumors recurred more quickly than did those that were estrogen receptor-positive (ER+) ($P = 0.0001$). In those women who were ER+ the addition of tamoxifen significantly improved the relapse-free survival. This occurred equally in pre- and postmenopausal patients. On the other hand, for ER− women no differences in any of the three regimens have been observed. No advantage for BCG immunotherapy can be observed.

Of interest is the fact that in premenopausal women CMF alone gave better results in ER+ women than in ER- women. On the other hand, in postmenopausal women CMF alone gave the same results in both ER+ and ER− patients. One interpretation of this data would be to support the hypothesis that CMF has a castration-mediated hormonal effect in premenopausal women. Alternate hypotheses would include differential tumor cell burdens and/or tumor cell kinetics and/or aggressiveness of therapy in pre- versus postmenopausal stage II lesions.

A variety of trials are in progress in which nonestablished control groups are used (Table 6). In these trials no regimen is used that had been clearly demonstrated to be of value, in even preliminary analysis, at the time of trial initiation. Three of these trials are those of the NSABP, which were all reported simultaneously due to the massive case accrual potential of this group. At this point there would appear to be little to justify L-PAM and 5-FU as a control for premenopausal women. On the other hand, if the preliminary results hold up, this combination may be of value in postmenopausal women with $\geq$ 4+ nodes.

Table 14. Estimated recurrence rates at 36 months in adjuvant study at Case-Western Reserve University. Estimated relapse-rates at 36 months, expressed as percentages

Patient characteristics	CMF	CMFT	CMFT + BCG
All patients	51.8	59.5	45.1
ER +	35.2	30.1	26.2

The current Milan trial in postmenopausal women is based on a hypothesis published by Norton and Simon [25]. This hypothesis can be summarized as follows: (1) human tumors grow in a Gompertzian fashion. For such growth the growth fraction of the tumor cells is maximum at the time of initiation of growth, while the growth rate is smallest for both tiny and very large tumors. The maximal growth rate occurs when the tumor is about 37% of its limiting size, which is the inflection point of the growth curve; (2) the maximum sensitivity to chemotherapy is at the inflection point and is less for very small and very large tumors. If this hypothesis is correct it would be best to give moderately intensive drug therapy initially (tumor above its inflection point) and when complete remission is achieved intensify the treatment. This late intensification would be required since the small residual tumor would be below the inflection point and less sensitive.

In the current Milan trial for postmenopausal women one group receives six cycles of CMF plus prednisone (CMFP) followed by four cycles of adriamycin plus vincristine (AV). A second group receives the sequential CMFP and AV beginning with lower doses which progressively increase toward a maximum at the last cycle (Table 6). To avoid excessive toxicity prednisone and vincristine are not intensified.

Four nonrandomized trials are outlined in Table 7. These trials utilize a variety of historical controls. These controls are either cases drawn from the same institution, from other groups or national end-results analysis. The appropriateness of these controls can be debated with much heat, but little light can be developed until longer follow-up exists.

At MD Anderson the adjuvant regimen has involved 5-fluorouracil, adriamycin, and cyclophosphamide (FAC) combined with BCG. Between January 1974 and April 1977 222 patients with stage II or III breast cancer have been treated with this regimen, beginning within 10 weeks of surgery. The surgery was heterogeneous, including radical or modified radical mastectomy (195 patients) and extended simple mastectomy (27 patients). All except 26 patients received postoperative irradiation. This group is compared for disease-free interval and survival with a historical control group consisting of 151 consecutive patients seen at MD Anderson Hospital between January 1972 and December 1973 with stage II or III breast cancer. The two groups were comparable in number of involved nodes and stage of disease. There were differences in distribution of patients by menopausal status, type of surgery, and race. In addition, median follow-up time is different, with a significantly shorter follow-up

in the historical controls. Therefore this historical control lacks the equivalent comparability observed in the prospectively randomized control groups of the NSABP and the Milan group. When a hazard ratio involving the usage of a Cox regression model was used the distribution of hazard between the chemotherapy and control groups was not significantly different.

The relapse-free survival at 30 months is 78% for the FAC-BCG group compared with 55% in the controls ($P < 0.01$) (Table 15). As can be seen, the number of premenopausal patients in the historical control group is extremely small (38) and no statistically significant benefit can be demonstrated for premenopausal women with 1–3+ nodes, the one group in whom L-PAM for 18 months is effective in the NSABP study. On the other hand, FAC-BCG appears to be effective in all the other situations, where L-PAM is not effective.

In terms of overall survival the chemotherapy group has an estimated 89% survival at 3 years, in comparison to 68% in the control group. Since the control group has a longer follow-up, survival in this group is less of an estimate, and more a reality, than in the adjuvant study group. When broken down by subsets the overall survival advantage for FAC-BCG mirrors the relapse-free survival advantage with only the premenopausal women with 1–3+ nodes not demonstrating any benefit.

The toxicity of this regimen was more significant than reported with other regimens. Nausea and vomiting were reported in 98% and alopecia in 95%. The median absolute granulocyte count was 2.4 for cycle 1 and 2.1 for cycle 6.

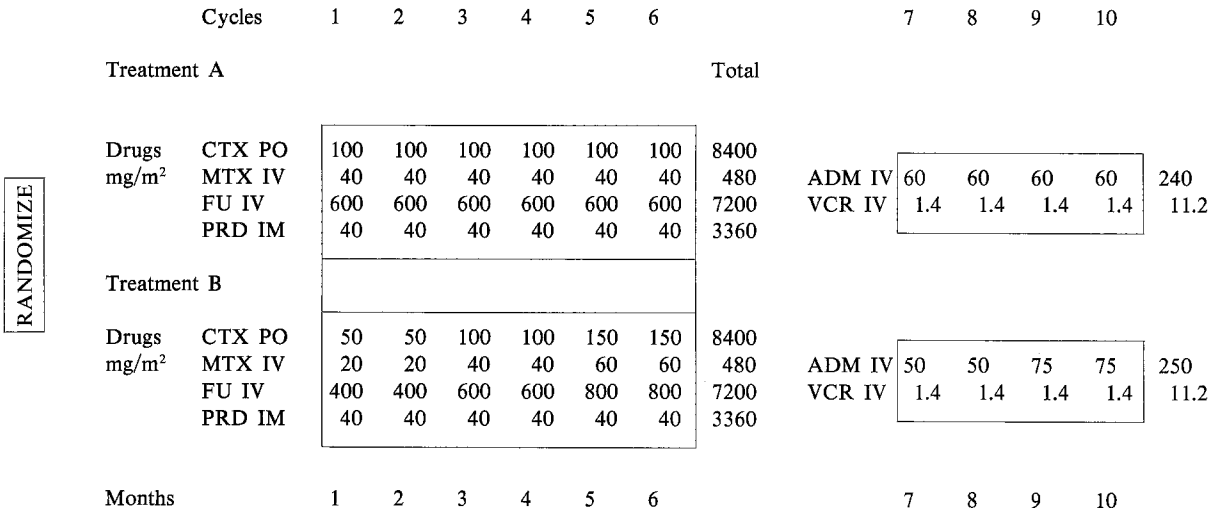


Table 15. FAC-BCG: Estimated relapse-free survival at 3 years

Characteristics	No. of patients	No. of recurrences	% Disease-free at 3 years	*P*-value
All patients				
Chemotherapy	222	41	78	
Control	151	76	55	< 0.01
Premenopausal 1–3+ nodes				
Chemotherapy	40	7	80	
Control	14	7	57	0.26
Premenopausal ≤ 4+ nodes				
Chemotherapy	60	15	65	
Control	24	16	37	< 0.01
Postmenopausal 1–3+ nodes				
Chemotherapy	34	3	91	
Control	46	17	70	0.04
Postmenopausal ≤ 4+ nodes				
Chemotherapy	88	16	79	
Control	67	36	48	< 0.01

Congestive heart failure was observed in three patients, possibly related to the use of adriamycin. Two of these patients symptomatically improved following digitalization, but one patient continues to require supportive care. Seventeen patients (8%) refused further treatment after receiving one or more cycles of chemotherapy.

At the University of Arizona adjuvant chemotherapy has involved the combination of adriamycin and cyclophosphamide. For stage I patients with negative nodes three cycles have been administered, consisting of adriamycin 30 mg/m^2 on day 1 and cyclophosphamide 150 mg/m^2 on days 3 through 6. Cycles were repeated every 3 weeks. For stage II and III patients with positive nodes eight courses were given, with randomization to receive radiation or not after the first two drug cycles. Between June 1974 and March 1979 a total of 248 patients were treated. Of these, 168 were fully eligible and evaluable and 80 were classified either as ineligible or partially evaluable.

For the stage I, negative-node, patients the median follow-up is 19–20 months and relapses have occurred in 3/68 (4%). For stage II patients with positive nodes relapses have occurred in 27/138, with a median follow-up of 25–27 months. In stage III patients the relapse-rate is 18/42 with a maximum median follow-up of 34 months. The relapse-free survival for stage II patients is projected out to 48 months and is compared to the CMF and control group of the Milan study of Bonadonna et al. It is superior in both pre- and postmenopausal patients but no comparability analysis has been made.

Richard Cooper, a community oncologist, has reported on his experience with adjuvant chemotherapy with the help of James Holland and Oliver Glidewell. The regimen used is CMFVP, originally described by Cooper for use in advanced disease. One hundred women with four or more positive nodes after radical or modified radical mastectomy were treated between 1968 and 1973. Twenty-seven had postoperative irradiation and 73 did not. The CMFVP was administered for 9 months. The median observation period, at the time of reporting, was 5½ years, 65 of the 100 patients having been observed for 5 years or more. The historical controls used for analysis in the paper are the NSABP surgical control from the thio-Tepa study and data on 21,084 women with regional metastases collected in the end-results program of the national cancer institute. The results in the 100 women are clearly superior to the results in these historical controls in terms of relapse-free survival and overall survival at 5 years. The 27 women who were irradiated did significantly worse than the 73 who were not.

What positive therapeutic implications can be drawn from all the adjuvant studies that have been undertaken to date? These are listed in Table 16. Obviously not all these implications will be equally valid and they cannot all be given equal weight. The relative weight that is given to any of these implications will be an individual process by informed clinicians. Each individual will weigh factors such as the appropriateness of the study design, the follow-up time, the quality of the data, and the track record of the investigators. At this point one can have opinions about the optimal experimental design but there is no definitive proof of value for one approach over an other. The ultimate worth of a study will be determined by its reproducibility and the impact it has on improving patient care and end results. Since the adjuvant treatment of breast cancer is still a half-way technology, repetitive

Table 16. Positive therapeutic implications from breast cancer adjuvant trials

I. From prospectively randomized trials with a surgery-only control prior to 1970
   1. One cycle of cyclophosphamide is of benefit for pre- and postmenopausal women without positive nodes in terms of relapse-free survival (RFS) and overall survival (OS). For women with positive nodes it is positive only in terms of RFS
   2. One cycle of thio-Tepa is of benefit to premenopausal women with ≥ 4+ nodes in terms of RFS and OS

II. From prospectively randomized trials with a surgery-only control initiated after 1970
   1. 18 months of L-PAM is of benefit to premenopausal women with 1–3+ nodes in terms of RFS
   2. 12 cycles of CMF is of benefit to all premenopausal women with positive nodes in terms of RFS and OS
   3. 6 cycles of LMF + 18 months of BCG is of benefit to node-negative women in terms of RFS at 3 years

III. Prospectively randomized trials with L-PAM as control
   1. L-PAM + 5-FU is superior to L-PAM in postmenopausal women with ≥ 4+ nodes in terms of RFS at 3 years
   2. CMFVP is superior to L-PAM in pre- and postmenopausal women with positive nodes in terms of RFS at 2 years
   3. CFP ± irradiation is superior to L-PAM in premenopausal women with positive nodes in terms of RFS at 3 years

IV. Prospectively randomized trials with CMF as the control
   1. Six cycles of CMF is equivalent to 12 cycles CMF for premenopausal women in terms of RFS and OS at 3 years
   2. CMF + tamoxifen is superior to CMF in all pre- and postmenopausal women with positive nodes who are ER+

V. Prospectively randomized trials with a nonestablished control group None as yet

VI. Nonrandomized Trials
   1. FAC-BCG is effective in pre- and postmenopausal women with positive nodes in terms of RFS and OS at 3 years
   2. CMFVP is effective in premenopausal women with ≥ 4+ nodes in terms of RFS and OS at 5 years
   3. 8 cycles of adriamycin plus cytoxan is effective in stage II pre- and postmenopausal women with positive nodes in terms of RFS at 2–3 years

confirmatory trials do not have a high priority. What is preferred are new trials, which build upon the older trials, and attempt to continue the improvements in end results. The optimal conclusion of this clinical research will be reached when a totally effective, nontoxic therapy is found. One problem in this ongoing strategy of attempts to continually improve the results is that new studies must be designed before older studies are fully analyzable. Therefore educated guesses as to an appropriate control must be made. Through the clarity of retrospective vision it now seems obvious that L-PAM or L-PAM + 5-FU are not optimal control regimens for postmenopausal and premenopausal women, respectively. We can only hope that the utilization of historical controls from earlier studies will enable meaningful interpretation of the results to be made.

What has been learned from past experience is that caution should be exercised in interpreting trials with only projections of 2- to 3-year relapse-rate survival. Only with much longer follow-up will the full cost-benefit analysis be determinable (Table 17).

In adjuvant chemotherapy there remains a series of unresolved questions, which hopefully will be answered by the many major trials currently under way. One question is how to explain the differential effect of adjuvant drug treatment in premenopausal and postmenopausal women. The most facile explanation is to implicate a hormonally mediated effect in premenopausal women. This is supported by the high percentage of premenopausal women who develop ammenorrhea while on adjuvant chemotherapy. It is also supported by laboratory studies showing significant hormonal changes being caused by the drugs [9]. The hypothesis loses ground when older studies of surgical or radiation prophylactic castration are examined since most have failed to demonstrate a 5-year survival advantage [20]. The widespread incorporation of estrogen receptor assays into adjuvant chemotherapy studies may help to solve the dilemma. A positive hormonal effect from 'medical castration' would theoretically be retricted to premenopausal women who were ER+. Some support for this is given in a Case-Western Reserve University study. As indicated earlier in this study CMF alone was compared with CMF + tamoxifen (CMFT) and CMF + tamoxifen plus BCG. All patients had their estrogen receptor status determined. Of great interest was the superior result in terms of relapse-free survival at 36 months for CMFT over CMF in ER+ women. Of greatest relevance to the question under discussion is the analysis of the data with CMF alone. In premenopausal women CMF results in ER+ women were superior to those in ER women. In postmenopausal women no such difference was observed. This would support a CMF effect being hormonally mediated in premenopausal women. It would tend to reject the hypothesis that ER+ women are more intrinsically responsive to chemotherapy. If this were so the superiority for CMF in ER+ women should have been observed in postmenopausal women as well. The major problem in this study in ascribing full support to the hormone hypothesis of CMF action is the lack of surgery-only control. It may be that CMF is also effective in ER− women, but this can only be related to historical control data. It still also remains hard to understand why an imperfect medical castration would be superior to the sure-fire surgical castration approach. More aggressive regimens do appear to be giving positive results in postmenopausal women, and if these hold up in long-term analysis it may make the debate about the hormonal impact of CMF in premenopausal women academic.

The Toronto study of Meakin et al. [27] has been stated to be supportive of the hormonal interpretation but is in fact not definitive in answering the critical questions regarding the value of adjuvant castration in premenopausal women (Table 18). Castration alone was not of benefit to the younger (< 45 years) premenopausal women. The only group to achieve benefit received long-term prednisone after castration; these were premeno-

Table 17. The cost-benefit analysis in adjuvant trials

	Benefit	Cost
Early	1) Relapse-free survival 2) Delay in recurrence	1) Acute toxicity 2) Economic cost 3) Psychosocial cost
Late	1) Overall survival 2) Pattern of relapse	1) Chronic organ damage 2) Second tumor development

Table 18. Ovarian irradiation and prednisone following surgery and radiotherapy for breast cancer. Data of Meakin et al. [20]

Premenopausal < 45

R — Surgery + X-ray + castration
R — Surgery + X-ray

Premenopausal > 45 years and postmenopausal

R — Surgery + X-ray + castration + prednisone
R — Surgery + X-ray + castration (7.5 mg/daily for up to 5 years)
R — Surgery + X-ray

1. Premenopausal < 45 years: no statistically significant benefit from castration in terms of delayed recurrence or survival
2. Premenopausal > 45 years: statistically significant benefit from castration + prednisone
3. No benefit for postmenopausal patients

pausal women over the age of 45. Since prednisone may exert a cytotoxic effect, it is difficult to ascribe all the therapeutic benefit to the ovarian oblation. Since this study predated the routine use of the estrogen receptor site assay, this valuable tool is not available for analysis of this study. The current study of the Eastern Cooperation Oncology Group comparing CMF with CMF + prednisone should yield valuable data on the role of prednisone, especially since all patients will have their ER status determined.

The current adjuvant study of Bonadonna and his group in premenopausal women, which compares 12 cycles of CMF with 6 cycles of CMF, has data on estrogen receptor activity available. An analysis has been done comparing relapse-free survival at 3 years in ER+ and ER− women (Table 19). No meaningful difference can be seen at this time. When the group of women with CMF-induced amenorrhea are evaluated separately the same result is observed. This analysis would not support the hypothesis that the adjuvant CMF effect is mediated through medical castration.

Kinetic factors have been shown to be associated with relapse after initial primary treatment. Meyer and Hixon [21] have studied the thymidine tumor labeling indices (TLI) and have found that a high TLI appears to be associated with rapid evolution of breast carcinoma both before and after diagnosis and treatment (Table 20). They studied the TLI in 133 patients with invasive primary lesions. Patients who initially had local or distant spread or who developed recurrent tumor had a higher geometric mean TLI (2.93) than did patients who were still free of disease (1.85) ($P < 0.05$). The TLIs ranged from 0.04 to 18.6, with a median of 2.21. Women with TLIs above the 2.21 median had a significantly higher rate of early recurrence of tumor than did patients with TLIs below ($P = 0.001$). Thirty-nine younger women (below the age of 50) had a higher geometric mean TLI (2.79) than did 89 women over the age of 50 (1.96). While menopausal data were not available, these findings suggest a tendency for carcinomas in premenopausal patients to have a higher TLI than those in postmenopausal patients.

Allegra et al. [2] have demonstrated that premenopausal women have a higher incidence of ER− assays on their primary lesions than do postmenopausal women (Table 21). Meyer et al. [22] have shown that ER− tumors have higher and more rapid proliferative states than do ER+ tumors. This is the explanation postulated for the prognostic importance of ER status as regards relapse after primary treatment. This could also explain why premenopausal patients do better with adjuvant chemotherapy.

Schiffer et al. [28] have studied the kinetics of human mammary tumors by in vitro methods. These have included tritiated thymidine labeling to measure the labeling index, and doubling labeling with triated thymidine and cytidine to measure DNA synthesis time and to estimate doubling time. When nodal positivity and labeling index were correlated, it was seen that younger women had a higher labeling index if they had positive nodes than if they had negative nodes (Table 22). In women with 1–3+

Table 19. Impact of ER status on relapse-free survival in premenopausal women CMF 12 vs CMF 6. Data of Tancini [31]

Premenopausal patients	
ER status	% RFS at 3 years
+	82.9
−	78.2 ($P = 0.23$)
CMF-induced amenorrhea	
+	87.2
−	77.5 ($P = 0.28$)

Table 20. TLI and outcome in primary breast cancer. Data of Meyer and Hixon [21]

Outcome	No. of patients	Geometric mean TLI	Mean tumor size (cm)	% with known positive nodes	Mean number of nodes
Dead with cancer	23	2.70	3.7	84	5.4
Alive with cancer	20	3.22	2.6	43	3.2
NED	83	1.85	2.2	31	1.1

Table 21. Estrogen receptor activity and menopausal status in primary breast cancer. Derived from Allegra et al. [2]

Estrogen receptor status	No. of patients	% Premenopausal	% Postmenopausal
Positive	103	21	79
Negative	79	46	54

Table 22. Relationship of age and positive axillary lymph nodes and cell kinetics in primary breast tumors. Derived from Schiffer [28]

Nodal status	Tritiated thymidine labeling index		
	≤ 49 years	≥ 50 years	P value
None positive	0.028	0.070	0.3
1–3+	0.084	0.043	0.04
≥ 4+	0.053	0.064	0.5

nodes the younger women (≤ 49) had a statistically significantly higher labeling index than did older women (≥ 50) ($P = 0.04$).

Another interpretation of the differential effect for adjuvant chemotherapy in pre- and postmenopausal patients can be based on the available cell kinetic studies. Silvestrini et al. [30] have shown that the labeling indices in premenopausal women with breast cancer are higher than those observed in postmenopausal women (Table 23). This is particularly true for premenopausal women who are ER−. This group has a mean labeling index of 9.49 ± 5.28. In comparison, postmenopausal women who were ER+ had a mean labeling index of only 2.64 ± 4.54. It is reasonable to assume that this latter group would have a diminished cell kill with an effective dose of drug than the younger women with the higher labeling index.

The potential impact of this kinetic difference would be enhanced by a differential in drug dosing with an effective regimen. This appears to have occurred in the Bonadonna study with CMF. In an updated analysis Bonadonna has found that those women who received 85% or more of the specified protocol doses had a significantly better relapse-free survival (79.3%) than did those who received below 55% of the optimal dose (50.0%) (Table 24). When this was subsetted by menopausal status a clear separation occurred (Table 25). Twice the proportion of premenopausal patients (26.2%) received ≥ 85% of optimal drug as compared with the postmenopausal group (13.5%). When those receiving < 55% of the dose were analyzed it turned out that this involved a quarter of the postmenopausal women but less than 10% of the younger group. Therefore a case can be made to support the statement that the younger women were more drug-responsive and received higher doses of CMF, while the older women were intrinsically less drug-responsive and received lower doses. This could be an explanation for superiority of adjuvant CMF in premenopausal as compared with postmenopausal women.

In summary, there are only three adjuvant chemotherapy studies with positive data that meet the following criteria: (1) prospectively randomized; (2) surgery-only control group; (3) data allow analysis of relapse-free survival and overall survival at 5 years; and (4) analysis for meaningful subsets is possible. These are the thio-Tepa and L-PAM studies of the NSABP and the CMF study of the Milan group. The cytoxan study of Nissen-Meyer is too diffuse and heterogeneous for meaningful evaluation by subsets. All three of these studies are negative in postmenopausal women but have some degree of positivity in premenopausal women. What is difficult to interpret is the dichotomy of results in the different subsets in women with 1–3+ nodes and ≥ 4+ nodes (Table 26). Why should one cycle of thio-Tepa be more effective than 18 months of L-PAM in women with ≥ 4+ nodes? Why should the opposite be true for the better-prognosis group with 1–3+ nodes. It is hard to explain with kinetic interpretations or with hormonally mediated interpretations, unless one assumes a different mix of prognostic variables, e.g., estrogen receptor activity in the studies.

Table 23. Correlation of ER status and labeling index.Data of Istituto Tumori, Milan [30]

Labeling index group	Menopausal status	ER status	No. of patients	Mean labeling index
Low	Post-	+	95	2.64 ± 4.54
Medium	Post-	−	33	4.26 ± 3.93
	Pre-	+	50	5.19 ± 5.80
High	Pre-	−	21	9.49 ± 5.28

Table 24. Relapse-free survival in CMF breast adjuvant study correlated with optimal dose. Data from Rossi et al. [27]

All patients	
% Optimal dose administered	% Disease-free
≥ 85	79.3
55–84	55.0 ($P = 0.04$)
≤ 55	50.0

Table 25. Optimal dosing of CMF in adjuvant chemotherapy of breast cancer. Data of Rossi et al. [27]

Percentage of patients receiving ≥ 85% of optimal drug dose
Premenopausal – 26.2
Postmenopausal – 13.5
Percentage of patients receiving < 55% of optimal drug dose
Premenopausal – 9.7
Postmenopausal – 25.0

Table 26. Adjuvant controlled studies in premenopausal breast cancer

Regimen	Positive in terms of RFS		Positive in terms	
	1–3 +	≥ 4+	1–3+	≥ 4+
Thio-Tepa 1 cycle	No	Yes	No	Yes
L-PAM 18 months	Yea	No	No	No
CMF 12 cycles	Yes	Yes	Yes	Yes

Table 27. Comparison of control groups in major adjuvant studies. Derived from Rossi et al. [27]. Relapse rate at 24 months expressed as percentage

Group	No. of patients	Total failure	Premenopausal			Postmenopausal		
			All	1.3+	≥ 4+	All	1.3+	≥ 4+
National surgical Adjuvant breast Project	169	31.4	36.7	25.8	48.3	28.4	16.1	41.5
National cancer Institute, Milan	179	36.5	42.2	32.1	65.4	31.3	28.8	44.4
MD Anderson Hospital	151	35.0	–	30.0	60.0	–	22.0	38.0
Swiss Group OSAKO	57	33.3	35.5	–	–	30.8	–	–
Multi-Center British group	128	39.9	43.2	–	–	38.1	–	–

Many of the adjuvant chemotherapy currently in progress no longer contain a control group treated by surgery only. These protocols compare two or more chemotherapeutic regimens with or without additional hormonal therapy or immunotherapy. The results of these studies will have been compared with surgery-only control groups of the earlier studies to establish some reasonable frame of reference for progress. This will be especially true if the differences between treatment groups in these studies are small and clearly evident major therapeutic breakthroughs are not achieved. This comparison with older control groups will be complicated by the fact that these older studies did not include analysis of estrogen receptor activity. Rossi et al. [27] have attempted a comparison of five surgery-only 'control' groups (Table 28). The only comparison possible is for relapse rate at 2 years. What is encouraging is that there does appear to be reasonable comparability in all these studies.

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