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Adjuvant Chemo(immuno-)-therapy of Primary Breast Cancer with Adriamycin–Cyclophosphamide (and Levamisole)—Six-year Evaluation*

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Abstract—*In a phase II-type study 52 patients with no signs of metastases but with a high risk of recurrence were treated with 6 courses of adriamycin–cyclophosphamide as adjuvent systemic therapy following modified radical mastectomy of primary breast cancer. Half of the patients were randomized to receive additional immunotherapy with levamisole for 2 yr. The scheduled dose and time regimen could be achieved in over 90% of patients. A comparison of the actuarial disease-free and overall survival with data reported in the literature indicates a similar positive effect of adjuvant systemic therapy as described in adjuvant studies using polychemotherapy regimens. Immunotherapy with levamisole had no effect on disease-free and overall survival but added to general toxicity. Particular attention was paid to psychological consequences of adjuvant systemic therapy; consistent attention by one specifically trained physician during the whole therapy and follow-up period was effective in coping with the emotional problems. The difficulties in treating recurrences after adjuvant therapy became apparent. A high rate of loco-regional recurrences and of cerebral metastases was noted.*

INTRODUCTION

IN 1975 the first results of two pioneering studies on the effect of adjuvant chemotherapy in patients with operable breast cancer using l-phenylalanine mustard [1] and CMF [2] were published and stimulated an unabating wave of research on this subject. In June 1976 a Cooperative Group at the University of Ulm initiated a study on adjuvant therapy of breast cancer with the aim of testing in a phase II study a more aggressive cytotoxic regimen, adriamycin–cyclophosphamide (ADR–CPA), which had been reported to show superior results in metastatic breast cancer [3], and to search for a beneficial effect of immunomodulatory therapy by randomizing half of the patients to receive levamisole, which was alleged to have produced improved survival in advanced breast cancer [4]. Preliminary clinical evaluations of this study have been reported [5, 6]; in addition, the short- and long-term effects of this type of adjuvant chemotherapy on the hematological system [7–9] and on the immune system [10] have been published. This report represents the clinical data on the patient group 6 yr after initiation of this study.

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MATERIALS AND METHODS

Patients

From 1 June 1976 through March 1979 54 consecutive patients were entered into the study of whom 52 completed chemotherapy and are fully evaluable. The present evaluation was performed as of 31 May 1982, 6 yr after admission of the first patient. All patients fulfilled the following criteria: histologically proven breast cancer removed by modified radical mastectomy; high risk of recurrence as defined by involvement of homolateral axillary lymph nodes (T_{1-3}, N_+), or by tumor size or location (T_3, pN_0 with lateral primary, or T_{2-3}, pN_0 with central or medial primary tumor); age $\leqslant 68$ yr; no other malignant tumor; exclusion of recognizable metastatic disease by careful clinical examination, laboratory test, chest X-ray, bone scan, liver scan or upper

gastrointestinal sonography; normal hemopoietic and renal function; no cardiac disorders obviating the use of adriamycin.

Informed consent

Patients were informed of the aims and risks of the proposed adjuvant therapy and gave written consent. The study protocol was reviewed and approved by the Ethics Committee of the University of Ulm.

Chemotherapy

All patients were to receive 6 courses of adriamycin (50 mg/m^2) plus cyclophosphamide (500 mg/m^2), administered intravenously at intervals of 4 weeks. Adjuvant therapy was started between 2 and 3 weeks after mastectomy. With a granulocyte count below 3000/mm^3 or a platelet count below 150 000/mm^3 at the scheduled time for the next course treatment was delayed for 1–2 weeks, but full doses were given whenever possible.

Immunotherapy

All patients were stratified according to the extent of the primary disease into 4 strata (lateral tumor, $N_{<4}$; lateral tumor, $N_{\geq 4}$; medial or central tumor, $N_{<4}$; medial or central tumor, $N_{\geq 4}$) and randomized to receive either additional immunotherapy or no immunotherapy using a computer generated randomization plan (Department of Clinical Documentation). Levamisole was given at doses of 150 mg/day p.o. on days 14, 15 and 22, 23 of each course, and on 2 consecutive days of each week for an additional 18 months after completion of chemotherapy.

Statistical methods

The probability of disease-free survival and overall survival was estimated utilizing the actuarial life-table method of Kaplan and Meier [11]; differences for various subgroups were assessed for statistical significance using the log-rank test [12]. For comparison with results from the literature, survival data were also calculated for the subgroups of patients with positive axillary lymph nodes ($n = 42$) only.

RESULTS

Toxicity and total dose administered

Of the 54 patients entering the study 2 patients received no further treatment after the first course: 1 patient refused further therapy for intolerable subjective side-effects and has been lost from follow-up; the other patient experienced severe hemopoietic toxicity with agranulocytosis, thrombopenia and sepsis, but recovered fully and is free of disease until now. These 2 patients are not included in the analysis. The distribution between the group receiving additional immunomodulatory therapy and no immunotherapy was balanced between the 4 strata (I: 7/6; II: 4/2; III: 12/12; IV: 4/5). Of the 52 patients receiving the planned 6 courses of chemotherapy a delay of 1 course was necessary in 3 patients, a dose reduction in 2 patients and a dose reduction and delay during 2 courses in 1 patient for mucosal toxicity. Thus 46/52 patients received 100% of the planned dose within the scheduled time; 3 further patients received the full dose with a maximum delay of 2 weeks; in the 3 patients with dose modification cumulative doses ranged from 83.3 to 95.8% of the planned dose.

Disease-free survival

Figure 1 gives the actuarial survival curves for disease-free survival for the whole group, for pre- and postmenopausal patients, and for the groups with and without levamisole. The probability of recurrence appears to be slightly higher for postmenopausal patients; however, this difference did not reach statistical significance in the log-rank test ($\chi^2 = 0.888$). The addition of levamisole did not influence the recurrence rate in the two groups ($\chi^2 = 0.065$). The curve for disease-free survival for the subgroup of patients with positive axillary lymph nodes only ($n = 42$) is virtually identical to the total group ($\chi^2 = 0.00092$).

Overall survival

Actuarial survival curves for overall survival are shown in Fig. 2 for the whole group and the relevant subgroups. Here the log-rank test for comparing the premenopausal and the postmenopausal groups reaches statistical significance ($\chi^2 = 3.167$; $P < 0.1$). There was no difference between the group receiving levamisole and that without immunotherapy ($\chi^2 = 0.258$). Again, the survival curve for the N_+ only patients was identical to the total group ($\chi^2 = 0.000094$).

Pattern of relapse and results of salvage therapy

Out of the 52 patients 23 have relapsed. In Table 1 the patients that relapsed are grouped in a rank order according to initial tumor mass; time and site of recurrence, type of salvage treatment and results of therapy are given. Eleven patients, i.e. 21% of the total group, experienced locoregional recurrence, which in 7 cases has so far been the only site of recurrent disease. The survival of the relapsing patients from time of recurrence is shown in Fig. 3. Median survival is 15 months. Of

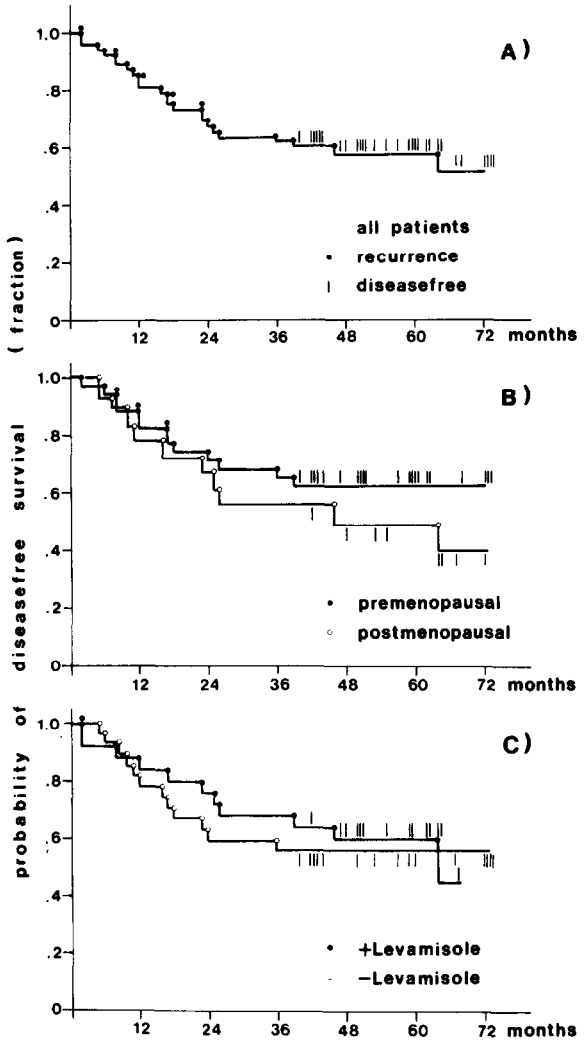

Fig. 1. Probability of disease-free survival for: (A) all patients (n = 52); *(B) premenopausal* (n = 34) *and postmenopausal* (n = 18) *patients; and (C) patients with levamisole* (n = 25) *and without levamisole* (n = 27). *The dots indicate recurrences, the vertical bars patients without recurrent disease.*

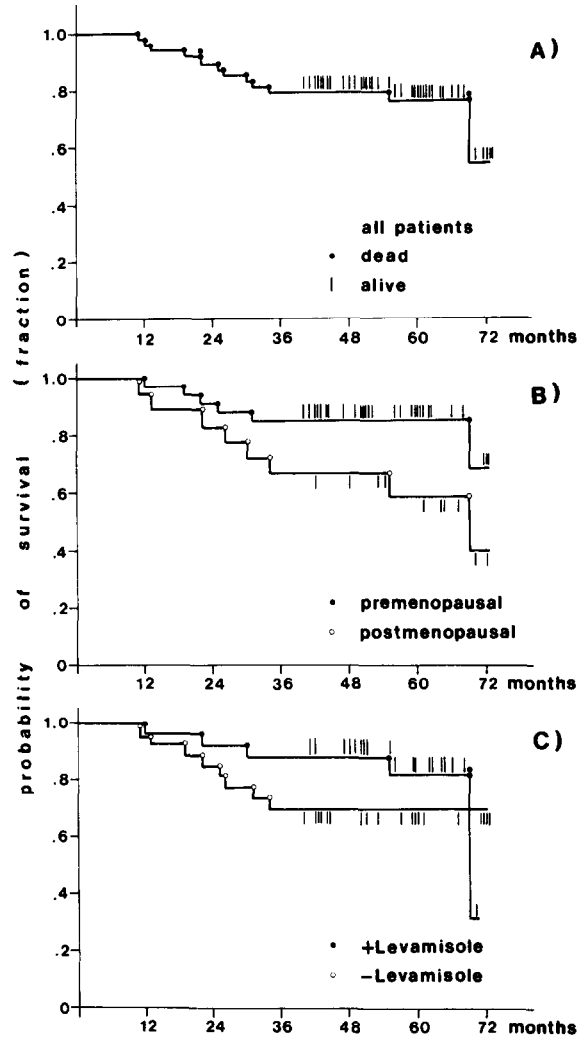

Fig. 2. Probability of overall survival for the same groups as in Fig. 1.

the five patients still alive for more than 24 months after recurrence all had locoregional disease treated by surgery and/or radiotherapy and hormonal treatment.

Side-effects

Hematological side-effects of the cytotoxic regimen have been studied and described in detail [7–9]; while the short-term hematotoxicity was found to follow a predictable pattern of early depression and regeneration, a long-lasting defect in the granulopoietic system was found when the more immature compartments of the granulopoiesis were studied. Also, the immunological changes have been thoroughly reported [10]. Other clinical side-effects were recorded on a questionnaire comprising 10 items at the end of each course, and the severity of the side-effects was rated on an arbitrary scale (0–4); this evaluation was done by one person of the team (the psychotherapeutically trained physician). For those side-effects for which more than an occasional entry was made the results of the questionnaire are given in Table 2. The questions for infection, bleeding, neurological symptoms and respiratory distress did not reveal noteworthy side-effects of this therapy.

Of particular importance were those side-effects which were found only in the levamisole-treated group and which could be attributed to this drug by additional clinical evidence: these symptoms were most severe on the days of levamisole therapy or immediately thereafter, and they subsided after discontinuation of levamisole. These side-effects were of rheumatoid character in 8 patients with joint pain, stiffness, and swelling of hands and feet; these symptoms were accompanied by fever in 2 patients. Two patients experienced a disturbance of taste and burning of the tongue. In 6 patients discontinuation of levamisole was

Table 1. Characteristics of the patients with recurrent disease

Stage	NED	Pat.	Recurrences Site of recurrence loc/reg	soft t.	bone	visc.	Months from primary tumor	Therapy	Survival from 1st rec
$T_2 N_0$	5/6								
		So.			+		46	horm.	23
$T_3 N_0$	1/5								
		To.	+				2	op. +rad., NED	46+
		Bo.	+		+		16/22	op., chemo.	19
		Ba.			+		23	(chemo.)	4
		Grö.				lung	26	horm. chemo.	5
$T_1 N_{<4}$	5/7								
		Hö.	+				57	op. +rad. +horm.	3+
		Gro.	+		+		64	horm.	6+
$T_1 N_{\geq 4}$	3/3								
$T_2 N_{<4}$	8/16								
		Ho.				ZNS	10	horm.	2
		Dy.		con. br.	+		12	horm.	57
		Schei.		skin		lung, ov.	12	horm. chemo.	8
		Fu.			+		17	rad., chemo.	11
		Wa.	+				23	op. +rad., horm.	33+
		Ka.	+				24	op. +rad., NED	26+
		Kö.			+	+	36	horm.	8+
		Her.	+				39	horm.	2+
$T_2 N_{\geq 4}$									
		Ru.	+				8	rad., horm., NED	50+
		Hey.				lu. ZNS	11/13	horm.	4
		Be.	+				17	op. +rad., NED	48+
$T_3 N_=$	3/8								
		Th.				lu. ZNS	2/6	chemo.	11
		Mü.				lu. ZNS	6	chemo.	16
		Vo.				lu. ZNS	8/18	horm.	15
		Sch.	+		+		18	horm.	8
		Lu.	+	+		ZNS	25/53	op. +rad., chem.	31
Total	29/52	23	11	3	8	9			

NED: no evidence of disease; con. br.: contralateral breast; lu.: lung; ov.: ovaries.

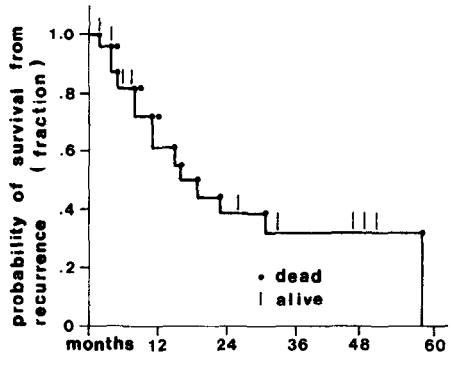

Fig. 3. Probability of survival from first recurrence for the 23 patients with recurrent disease.

necessitated by these symptoms during the second year of treatment.

Psychological consequences of adjuvant therapy

During the whole study phase all patients were treated and cared for by one member of the group (L. M.), who has had additional training as a psychotherapist. Continuous attention to psychological consequences revealed depression in nearly 80% of the patients with severe depression, necessitating the consultation of a psychiatrist in 3 cases. A retrospective psychosocial analysis on 38 surviving patients has been published elsewhere [13].

DISCUSSION

The particular regimen of adriamycin-cyclophosphamide had been chosen for a phase II study of adjuvant therapy of breast cancer at a time when first results with l-PAM [1] and CMF [2] became available; the clinical aims were firstly to evaluate the impact of a possibly more potent [3], short-termed regimen on patient compliance, and secondly to see whether this type of therapy appeared to be superior to less aggressive regimens and therefore should be tested in a randomized fashion.

A high degree of patient compliance could be achieved; the fact that only minimal schedule and dose adjustments had to be made indicates that the chosen combination is well tolerated by the patients included in this study.

Table 2. Evaluation of clinical side-effects by questionnaire

Side-effects	Results of questionnaire
Nausea/vomiting	All patients; moderate to severe (rating: 2.2 ± 0.6*)
Alopecia	All patients; complete or nearly complete
General fatigue	8 patients, mild to moderate (rating: 1.6 ± 0.7*)
Mucous membranes	Mild to moderate, 27 episodes in 11 patients
Diarrhoea	Mild to moderate, 15 episodes in 5 patients
Hemorrhagic cystitis	Mild to moderate, 6 episodes in 4 patients

Arbitrary scale: 0 = no complaints; 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening.
*Mean ± S.D. of 252 courses.

In general, studies on adjuvant systemic therapy indicate improvement for disease-free and overall survival for the studied population, and in particular for premenopausal patients [14, 15] and for patients with smaller tumor load [14, 16, 17]. In order to place the results of our phase II study into perspective with published data, Fig. 4 shows the disease-free and overall survival of our N_+ group in relation to the T_{1-2}, N_+ groups of the 'natural history data base' developed by Moon *et al.* [18] and to the results of 3 major adjuvant programs [19]. Although the inclusion of T_3 tumors imposes a poorer prognosis, our survival data segregate from the natural history data base and approach the results of the adjuvant study groups. Therefore our data of disease-free survival and overall survival indicate effectiveness of the used adjuvant regimen in the range of other published adjuvant regimens using combination chemotherapy.

Levamisole has been studied for a suggested immunomodulatory effect in breast cancer patients; while an increased remission rate and survival was reported in advanced breast cancer [4], the prognosis appeared to be negatively affected in a randomized adjuvant study [20]. In our study disease-free and overall survival were not significantly affected by levamisole (Figs 1 and 2). Subjective and objective side-effects were considerable. No case of levamisole-induced agranulocytosis has been observed in our patients, a side-effect of potentially serious consequences occasionally attributed to the drug [21]. Careful evaluation did not show any effect of levamisole on the cytotoxic drug-induced changes of granulopoiesis [22], nor on the immune status of these patients [10]. Therefore our data are in accordance with other studies which did not observe a positive effect of immunomodulatory therapy on the result of systemic adjuvant therapy [23–25].

The treatment of relapses after adjuvant therapy poses a serious oncological problem. There is limited published experience about the course of metastatic disease after failure of adjuvant therapy [26–29]. From the small group

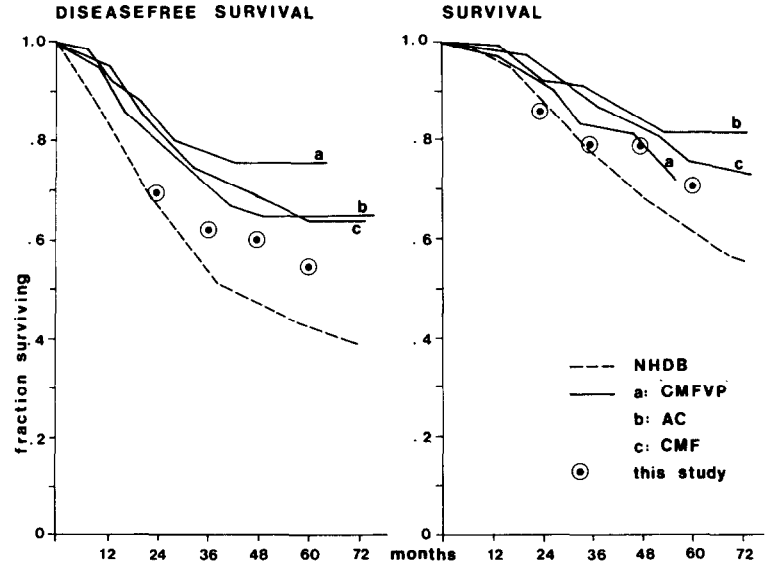

Fig. 4. Comparison of our data in T_{1-3}, N_+ patients to the survival curves of adjuvant studies and to a 'natural history data base (NHDB)' of T_{1-2}, N_+ patients [18]. *NHDB* (n = 796 [18]), *CMFVP* (n = 314 [16, 34]), *AC* (n = 159 [35]) *and CMF* (n = 645 [15]).

of patients in our study who relapsed during or after 6 courses of adriamycin-cyclophosphamide, the following tentative conclusions can be drawn (Table 1). Firstly, the probability of relapse appears to depend on the initial tumor burden; in particular, a large primary tumor carried a poor prognosis even when no axillary lymph nodes were involved. On the other hand, only 2/10 relapses occurred in the T_1, N_+ group. Secondly, the frequency of loco-regional recurrences was high (11/23) and evenly distributed throughout the prognostic groups (Table 1). If loco-regional recurrence was the only manifestation of disease, effective control by operation and/or radiotherapy could be achieved (Table 1). Thirdly, the high incidence (6/23) of cerebral metastases in our patients is noteworthy. Possibly, a chemotherapy-induced delay of tumor progression at extracerebral sites of micro-metastases allowed the time for development of cerebral metastases which were protected from the action of chemotherapeutic agents by the blood-brain barrier [30, 31]. Similar observations have been reported by Paterson *et al.* [32].

At the present time it is extremely difficult to define the contribution of various operative techniques, radiotherapy and adjuvant chemotherapy to the outcome of the primary therapy of breast cancer patients. The problem is aggravated by the developing recognition of the influence of prognostic factors [33]. The adjuvant systemic therapy is an option to improve the prognosis of breast cancer patients. However, the cost of such treatment, in particular with respect to psychosocial problems and to possible late effects, e.g. on the hemopoietic system [7, 8], should be kept in mind.

REFERENCES

1. FISHER B, CARBONE P, ECONOMOU SG *et al.* l-Phenylalanine mustard (l-PAM) in the management of primary breast cancer: a report of early findings. *N Engl J Med* 1975, **292**, 117–122.
2. BONADONNA G, BRUSAMOLINO E, VALAGUSSA E. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 1976, **294**, 405–410.
3. JONES SE, DURIE BG, SALMON SE. Combination chemotherapy with adriamycin and cyclophosphamide for advanced breast cancer. *Cancer* 1975, **36**, 90–97.
4. ROJAS AF, MICKIEWICZ E, FEIERSTEIN JN, GLAIT H, OLIVARI AJ. Levamisole in advanced human breast cancer. *Lancet* 1976, **i**, 211–215.
5. SCHREML W, BETZLER M, LANG M *et al.* Adjuvant intermittent chemo-immunotherapy of breast cancer. A prospective study. In: MOURIDSEN HT, PALSHOF T,A eds. *Breast Cancer: Experimental and Clinical Aspects.* Oxford, Pergamon Press, 1980, 165–168.
6. BETZLER M, SCHREML W, LANG M *et al.* Adjuvant intermittent chemo-immunotherapy for primary breast cancer: a prospective study with immunologic follow-up. *Recent Results Cancer Res* 1982, **80**, 185–191.
7. LOHRMANN HP, SCHREML W, LANG M, BETZLER M, FLIEDNER TM, HEIMPEL H. Changes of granulopoiesis during and after adjuvant chemotherapy of breast cancer. *Br J Haematol* 1978, **40**, 369–381.
8. SCHREML W, LOHRMANN HP. Hematotoxicity of adjuvant chemotherapy. In: JONES SE, SALMON SE, eds. *Adjuvant Therapy of Cancer II.* New York, Grune & Stratton, 1979, 63–70.
9. SCHREML W, KUBITZA P, LOHRMANN HP. Attempt at quantification of the cytotoxic drug-induced changes of the human bone marrow compartments. *Scand J Haematol* 1982, **28**, 151–162.
10. BETZLER M, FLAD HD, SCHREML W *et al.* Quantitative and functional studies of lymphocyte subpopulations during adjuvant chemo (immuno) therapy in patients with breast cancer. In: FLAD HD, HERFARTH C, BETZLER M, eds. *Immunodiagnosis and Immunotherapy of Malignant Tumors.* Berlin, Springer Verlag, 1979, 216–225.
11. KAPLAN EL, MEIER P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958, **53**, 457–481.
12. PETO R, PIKE MC, ARMITAGE T *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977, **35**, 1–39.
13. LANG M, MERGEL H, SCHREML W, KÖHLE K. Beobachtungen zur psychischen Verarbeitung adjuvanter Chemotherapie bei Mamma-Carzinom-Patientinnen. *Münch Med Wschr* 1983, **125**, 190–192.
14. FISHER B, REDMOND C, WOLMARK N, WIEAND HS. Disease-free survival at intervals during and following completion of adjuvant chemotherapy; the NSABP experience from three breast cancer protocols. *Cancer* 1981, **48**, 1273–1280.

15. BONADONNA G, VALAGUSSA P, ROSSI A *et al.* Multimodal therapy with CMF in resectable breast cancer with positive axillary nodes. The Milan Institute experience. In: SALMON SE, JONES SE, eds. *Adjuvant Therapy of Cancer III.* New York, Grune & Stratton, 1981, 435–444.
16. GLUCKSBERG H, RIVKIN SE, RASMUSSEN S *et al.* Combination chemotherapy (CMFVP) versus l-phenylalanine mustard (l-PAM) for operable breast cancer with positive axillary nodes. *Cancer* 1982, **50**, 423–434.
17. SENN JH, JUNGI FW, AMGWERD R. Chemo(immuno)therapy with LMF + BCG in node-negative and node-positive breast cancer. In: SALMON SE, JONES SE, eds. *Adjuvant Therapy of Cancer III.* New York, Grune & Stratton, 1981, 385–393.
18. MOON TE, JONES SE, DAVIS SL *et al.* Development of a natural history data base for breast cancer. In: SALMON SE, JONES SE, eds. *Adjuvant Therapy of Cancer III.* New York, Grune & Stratton, 1981, 471–481.
19. JONES S, MOON T, DAVIS S *et al.* Comparative analysis of selected breast cancer adjuvant trials in relation to the natural history data base (NHDB). In: SALMON SE, JONES SE, eds. *Adjuvant Therapy of Cancer III.* New York, Grune & Stratton, 1981, 483–491.
20. EXECUTIVE COMMITTEE OF THE DANISH BREAST COOPERATIVE GROUP. Increased breast-cancer recurrence rate after adjuvant therapy with levamisole. *Lancet* 1980, **ii**, 824–827.
21. SYMOENS J, ROSENTHAL M. Levamisole in the modulation of the immune response: the current experimental and clinical state. *J Reticuloendothel Soc* 1977, **21**, 175–221.
22. SCHREML W, LOHRMANN HP. No effects of levamisole on cytotoxic drug-induced changes of human granulopoiesis. *Blut* 1979, **38**, 331–336.
23. SERROU B, SANCHO-GARNIER H, CAPPELAERE P. Follow-up results from a randomized trial for T_3 and T_4 breast cancer patients: previous BCG immunotherapy improves response to chemotherapy in the relapse patient. *Recent Results Cancer Res* 1982, **80**, 157–161.
24. HUBAY CA, PEARSON OH, MARSHALL JS *et al.* Adjuvant chemotherapy, antiestrogen therapy, and immunotherapy for stage II breast cancer: 45-month follow-up of a prospective, randomized clinical trial. *Cancer* 1980, **46**, 2805–2808.
25. TORMEY DC, HOLLAND JF, WEINBERG V *et al.* 5-drug vs 3-drug ± MER postoperative chemotherapy for mammary carcinoma. In: SALMON SE, JONES SE, eds. *Adjuvant Therapy of Cancer III.* New York, Grune & Stratton, 1981, 377–384.
26. BONADONNA G, VALAGUSSA P, ROSSI A *et al.* Are surgical adjuvant trials altering the course of breast cancer? *Semin Oncol* 1978, **5**, 450–464.
27. WENDT AG, JONES SE, SALMON SE. Salvage treatment of patients relapsing after breast cancer adjuvant chemotherapy. *Cancer Treat Rep* 1980, **64**, 269–273.
28. BUZDAR AU, LEGHA SS, HORTOBAGYI GN *et al.* Management of breast cancer patients failing adjuvant chemotherapy with adriamycin-containing regimens. *Cancer* 1981, **47**, 2798–2802.
29. CHLEBOWSKI RT, WEINER JM, LUCE J *et al.* Significance of relapse after adjuvant treatment with combination chemotherapy or 5-fluorouracil alone in high-risk breast cancer. *Cancer Res* 1981, **41**, 4399–4403.
30. BENJAMIN RS, WIERNIK PH, BACHUR NR. Adriamycin chemotherapy: efficacy, safety, and pharmacological basis of an intermittent single high-dosage schedule. *Cancer* 1974, **33**, 19–24.
31. BOSSI A, COLOMBO T, DONELLI MG. Activity of cyclophosphamide and l-methylnitrosourea on Ehrlich carcinoma transplanted in different sites. Correlation between drug level and tumor inhibition. *Biochem Pharmacol* 1975, **24**, 21–26.
32. PATERSON AHG, AGARWAL M, LEES A, HANSON J, SZAFRAN O. Brain metastases in breast cancer patients receiving adjuvant chemotherapy. *Cancer* 1982, **49**, 651–654.
33. HENDERSON JC, CANELLOS GP. Cancer of the breast. The past decade. *N Engl J Med* 1980, **302**, 17–30, 78–90.
34. RIVKIN SE, GLUCKSBERG H, RASMUSSEN S. Adjuvant chemotherapy for operable breast cancer with positive axillary nodes: a comparison of CMFVP versus l-PAM. In: SALMON SE, JONES SE, eds. *Adjuvant Therapy of Cancer III.* New York, Grune & Stratton, 1981, 445–452.
35. ALLAN H, BROOKS R, JONES SE *et al.* Adjuvant treatment for stage II (node positive) breast cancer with adriamycin–cyclophosphamide (AC) ± radiotherapy (XRT). In: SALMON SE, JONES SE, eds. *Adjuvant Therapy of Cancer III.* New York, Grune & Stratton, 1981, 453–462.