Cancer Chemother. Pharmacol. 1, 187–195 (1978)

Cancer Chemotherapy and Pharmacology



*General Review*

# Adjuvant Chemotherapy in Breast Cancer: Critique and Perspectives

S. K. Carter

Northern California Cancer Program,
1801 Page Mill Road, Bldg. B, Suite 200, Palo Alto, California 94304, USA

The treatment of breast cancer has gone through several cycles. For a long time, the essence of all curative research was local control and the major thrust was to attempt to achieve this with radical surgery and radiotherapy. The apogee of this period was the super-radical mastectomy. A second cycle began with the use of long-term "adjuvant" systemic therapy. At the height of this cycle, when the promise seemed brightest, it appeared that systemic control would totally overwhelm the debate about local control. We now appear to be in a third cycle, where both local control and systemic control are important aspects of the debate on curative therapy. The local control emphasis has now switched to how *little* needs to be done to achieve this end. The object is to accomplish local control with maximal cosmesis, and the biological questions this raises are fundamental to the whole classic approach of surgical oncology. Systemic therapy is still highly important in the clinical research arena, but the less impressive results in postmenopausal women have made it evident that local control will still be critical. In addition, this finding has brought hormonal factors back into prominence, which, when combined with the new hormone receptor data, has made this area one of the most exciting for future research.

Breast cancer is a disease in which the data from clinical research studies are continuously impinging on the current state of the therapeutic art. A wave of enthusiasm for the potential of chemotherapy to significantly diminish the relapse rates after surgery and to reciprocally improve the survival of women with this dread tumor has just passed. Breast cancer was considered to be the best model for testing the basic hypothesis of the combined modality approach derived predominantly from rodent tumor studies.

Further follow-up on the reported adjuvant studies has now taken place. While these studies are still positive, they are no longer as dramatically positive as the early actuarial projections had led many to hope they would be. Despite the cautions expressed by the authors, the early data were greeted by a wave of publicity that assumed a dramatic breakthrough in therapy had clearly been established. The enthusiasm has now been dampened by the reality of the current analysis, and for some a dour pessimism has taken over, which may be as inappropriate as was the early great enthusiasm. We are still in an era of relatively short follow-up for a disease as chronic as breast cancer, and a large amount of data has still to be collected and analyzed. The purpose of this paper is to review the position at this moment in the continuum of studies of this disease with systemic therapeutic approaches.

In 1972, the National Cancer Institute launched a large-scale controlled trial of the use of chemotherapy as an adjuvant to surgery 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 [13]. Treatment failures occurred in 22% of 108 patients receiving placebo and in 9.3% of 103 women given L-phenylalanine mustard. This difference was statistically significant only for premenopausal women.

A follow-up of the NSABP data has shown that at 24 months of follow-up the percentage of treatment failures overall is 31.4% in 169 placebo patients and 23.5% in 179 L-PAM patients, the *P* value being only 0.06. When the data are broken down by menopausal status the picture is as follows:

| | Number of patients | % Treatment failure | *P* value |
|---|---|---|---|
| Age ≤ 49 | | | |
| Placebo | 60 | 36.7 | 0.06 |
| L-PAM | 59 | 22.0 | – |
| Age ≥ 50 | | | |
| Placebo | 109 | 28.4 | 0.28 |
| L-PAM | 120 | 24.2 | – |

0344-5704/78/0001/0187/$ 01.80

The only situation in which L-PAM shows a statistically significant superiority over placebo is with premenopausal patients with one to three positive nodes, where the failure rate is 25.8% with placebo in 31 patients as against 6.3% with L-PAM in 32 patients, with an average follow-up of 25–27 months ($P = 0.04$) [14].

What is clearly evident at this time is that therapeutic regimens may affect various subsets of patients differently. It will be essential to design studies so that adequate numbers of patients will be collected who are premenopausal, postmenopausal, have one to three positive nodes or four and more nodes, and are either estrogen receptor-positive or -negative. Analysis of each of these subsets will be essential, along with their potential interaction. Since there appears to be some variation in the rate of occurrence of treatment failure or mortality among subgroups, the time for determination of effectiveness may differ for various subsets. As Fisher has pointed out, the determination of effectiveness at the same time for the entire population or for each subgroup may therefore be misleading.

In 1973, Bonadonna, at the National Cancer Institute of Milan, began a study indentical with Fisher's, except that the chemotherapy was CMF (cytoxan, methotrexate, 5-FU), which had been found to be superior to L-PAM in advanced disease studies [2]. In only 5.3% of 207 women who received the CMF was there recurrence of cancer by the time of the first report, as opposed to 24% of 179 women who had surgery only. At the time of this first report, the patients in the study had been followed for an average of only 14 months.

In the most recent analysis of these data, which was made 3 years after mastectomy, the total failure time distribution was 45.7% in control patients, compared with 26.3% in women given CMF $P < 0.0001$ [3]. New disease manifestations were higher in the subgroup with four or more nodes (64.9% vs. 41.5%) than in the one with one to three nodes (37.9% vs. 19.1%). After 12 months of analysis, however, there was no difference in the recurrence rate for postmenopausal women. At 3 years, the failure rate in postmenopausal women was 40.1% in controls, as against 36.2% in the CMF group. When the control group is analyzed it is seen that premenopausal patients show a higher incidence of early recurrence than postmenopausal patients. In the CMF-treated women, the failure distribution was not different in the pre- and postmenopausal groups.

At the recently held American Society of Clinical Oncology meetings in Washington, D.C., Bonadonna gave a further update with four years of follow-up, with no essential difference in results. The data for postmenopausal women were still negative [4].

One possible explanation for this difference between pre- and postmenopausal patients is that in premenopausal patients there is a combination of a hormonally mediated cell kill and a cytotoxic cell kill, as 80% of the premenopausal patients treated with CMF developed amenorrhea, in some cases permanent and in others transient. Chemotherapy appears to effect a medical oophorectomy.

The potential importance of the hormonal effect in adjuvant studies can be seen in a study from Toronto reported by Meaken [19]. From 1965 to 1972, following mastectomy, premenopausal and postmenopausal patients aged 35–70 years, with or without histologically positive axillary nodes, received irradiation to the chest wall and regional nodal areas. They were then randomized to receive no further treatment, ovarian irradiation to a dose of 2,000 rad in 5 days, or (if 45 years or more) ovarian irradiation at the same dosage plus prednisone, 7.5 mg daily for up to 5 years. Patients entered in the study have been followed up for up to 10 years. Seven hundred seventy-nine patients were randomized into the study, 712 being eligible.

In the premenopausal patients aged less than 45 who were in clinical stage II or III, there was a persistent delay in recurrence for those given ovarian irradiation as against no treatment, but it never reached statistical significance ($P = 0.21$). In premenopausal patients age 45 or more, radiation to the ovaries plus prednisone delayed recurrence significantly compared with no treatment ($P = 0.01$). No differences in time before recurrence or survival were observed for postmenopausal patients.

The trial of prophylactic ovarian irradiation with and without prednisone from the Princess Margaret Hospital has important implications. The only benefit was observed in premenopausal patients aged 45 and over. It is interesting that in the CMF study the major impact on ovarian function was in the younger premenopausal group, and there is suggestive, but not conclusive, evidence that this group had the most benefit. The positive results in the Toronto study on women over 40 were also seen only after 3 years of follow-up. This is in direct contrast to the CMF and L-PAM data, where the benefit was seen initially. A late benefit could be explained by the therapy only working in patients with a small residual tumor cell burden or in a subset of slow-growing tumors. In either case, one would expect late relapses in these groups. It is important to emphasize that in the Toronto trial, the only variable that confers benefit is the addition of prednisone. This casts some doubt on the precise therapeutic role of ovarian ablation. Possible mechanisms of action of the prednisone could be: (1) adrenal cortical suppression; (2) an effect on prolactin produced by this suppression; (3) a direct effect on the pituitary; (4) an immunological effect, and (5) a direct antitumor effect. If adrenal cortical suppression is the important action, aminoglutethamide might be a superior way to achieve it, although high doses of prednisone must be given with this drug.

There have been several studies indicating that prophylactic oophorectomy can delay time to recurrence. Cole, in 1970 [10], reported on a prospective randomized trial of adjuvant X-ray castration in premenopausal and postmenopausal women. The hormonal ablation group showed a significantly prolonged recurrence-free interval compared with the control during the inital four years. In terms of 5-year survival, no benefit was observed. Nissen-Meyer [23] has also reported on a trial with adjuvant X-ray castration, which revealed benefit not only in the recurrence-free rate but also in the 4-year survival rate for the hormonal therapy.

In 1969, Nevinny et al. [22] reported on a trial of adjuvant oophorectomy. These authors also reported that the recurrence-free rate was prolonged. In the study of Ravdin et al. [25], the 18-month recurrence rate in the oophorectomy group with four or more positive nodes was only two-thirds that in the placebo group. The 5-year survival rate showed no difference, however, although the recurrence-free rate advantage was maintained for 3 years. These studies all give evidence that ovarian ablation can delay the onset of recurrence in women who have probable microscopically disseminated disease by up to 4 years, if not longer.

Rose and Davis have studied the hormonal impact of adjuvant chemotherapy [26]. In patients receiving either adjuvant L-PAM or a four-drug combination of CMF plus vincristine they observed that levels of circulating estrogens, follicle-stimulating hormones, and luteinizing hormones were affected in premenopausal women. In addition, they saw a significant decrease in plasma prolactin response following thyrotropic releasing hormone stimulation [11].

It appears that across-the-board use of prophylactic castration will not be of benefit to an overall group. The hormone receptor study may offer a new dimension on the subject. It might turn out that prophylactic oophorectomy would be beneficial for a subset of premenopausal women with positive assays for estrogen-binding protein.

Knight et al. [16] have reported on the prognostic importance of the estrogen receptor assay in 145 women who underwent modified or radical mastectomy for potentially curable breast cancer. The dextran-coated charcoal assay was used, with results of greater than 10 fmol 1 mg cytosol protein being considered positive. They found a statistically significant increase in the incidence of early recurrence in those patients with ER− primary tumors with a median follow-up time of 16–18 months. This was found to be true regardless of age or lymph node status.

In a more recent report by Knight et al. [17], with a median follow-up of 20 months, recurrences were documented in 37% of ER−, as against 15% of ER+, women ($P \leq 0.01$). Deaths have occurred in 20% of ER− and 6% of ER+ ($P \leq 0.01$). Of the patients with axillary node involvement, 10/29 ER− and 5/54 ER+ have died of breast cancer (35% vs. 11%, $P \leq 0.05$). The estrogen receptor assay was a potent prognostic variable for both pre- and postmenopausal patients.

Meyer and Bauer [20] have reported that primary breast tumors with a high growth fraction, as represented by a high thymidine labeling index, are more subject to early recurrence and more likely to respond to chemotherapy [18]. In the study of Knight et al. it was seen that ER− tumors with associated early recurrence were more common in premenopausal patients than in postmenopausal patients. This might help explain why adjuvant chemotherapy is more effective in premenopausal women than in postmenopausal.

At the University of Arizona, a study has been started to evaluate adriamycin and cyclophosphamide either with or without postoperative radiation as an adjuvant to surgery for women with stage II breast cancer. To date, relapses have occurred in 2 of 36 patients with one to three positive axillary nodes and in 0/27 with four or more involved nodes, with a median follow-up of only 18 months. In addition, 8/24 patients with stage III breast cancer treated in a similar fashion have relapsed during a median observation period of 22 months after surgery [28].

Another regimen being used in adjuvant study is the FAC regimen of the M.D. Anderson Hospital, which consists of 5-FU 400 mg/m$^2$ IV on days 1 and 8, adriamycin 40 mg/m$^2$ on day 1, and cyclophosphamide 400 mg/m$^2$ on 1 [7]. This regimen, combined with Connaught BCG, has been administered to 190 women with stage II and III breast cancer after surgery and postoperative radiation. In 131 patients who have been followed for more than one year, 17 relapses have been observed. When compared with a historical control group of 151 patients the results appear superior, but follow-up is still not long enough for a definitive conclusion.

The M.D. Anderson study differs from many other studies in that stage III cases were included if considered operable. This included patients with skin ulceration or fixation to deep muscle. Inflammatory breast cancer was *not* included. Most patients received postoperative radiation. A total of 131 patients were treated with adjuvant FAC-BCG from January 1974 to October 1976. Radiation therapy was usually started within two weeks of mastectomy and completed within five weeks. Radiation doses and ports are not given in the paper. Chemoimmunotherapy was started within 2–3 weeks of completion of radiation. The historical control group contained all patients who were operated on between January 1972 and December 1973 with stage II and III disease and at least one involved node at the time of surgery. This applied to 151 patients.

At the time of the last literature report, the control group had a median follow-up of 31 months, as compared to a 13-month median for the treated group. This longer follow-up in the control group is a sine qua non of most historically controlled studies. This is one reason why the treated test group appears to be doing better, as early actuarial analysis seems to be on the optimistic side when compared with the data when all patients have actually been followed up for longer periods.

When the distribution of patient characteristics possibly related to prognosis was examined the two groups were not evenly matched. The control group had a significantly higher percentage of patients aged 50 years and over, both pre- or postmenopausal, and of patients with primaries larger than 5 cm and stage III disease. Therefore, some imbalances favored the control group and others the FAC-BCG group.

At this time relapse-free survival favors the FAC-BCG group. Ninty-one percent of the FAC-BCG patients are disease-free (median follow-up 13 months), as against 69% in the control group with longer follow-up. Differences between control and FAC-BCG groups in disease-free survival were not statistically significant for those with primary tumors of less than 3 cm or with one to three involved nodes.

The Mayo Clinic [1] is currently conducting a three-arm adjuvant study to compare radical or modified radical mastectomy plus L-PAM, CFP (cyclophosphamide, 5-fluorouracil, prednisone), or postoperative radiotherapy plus CFP. The preliminary results show that relapse-free survival is shorter for premenopausal women treated with CFP ± radiation rather than L-PAM. No difference is seen in postmenopausal women. This study is of interest because it controls for postoperative radiation and the fields of radiation include the internal mammary chain. Since the chemotherapy includes prednisone, there is one arm of treatment that hits the controversial internal mammary chain with radiation and combines the adrenal suppressing effect of prednisone with chemotherapy, which may be acting upon ovarian function.

One of the neglected areas of research has been the psychosocial impact of adjuvant chemotherapy for breast cancer. The UCLA group has attempted to study this and has posed the question as to whether the delay in recurrence and/or increase in survival compensate for the toxicity, inconvenience, and expense of adjuvant drug treatment [21]. They interviewed 50 patients receiving chemoimmunotherapy with CMF plus BCG and/or cells. The patients had been treated for an average of 11 months and none had developed evidence of recurrent disease. The interviews lasted 30 min with a standard format, and the impact of adjuvant chemotherapy on five areas was explored. These were marital family relationships, sexual relationships, financial situation, general activity, and paid job and/or housework.

In 24% of cases, disruption of marital family relationships was claimed as a result of the treatment, but the exact opposite was claimed in an equal number. In 17% sexual activity was markedly diminished, and this was not improved in any cases. The largest impact was on financial burden, where 54% reported that this was a significant problem. This expense ranged from $2,500 to $13,800 per year. Of those with paid jobs, 60% lost 10 days per year secondary to the therapy and 45% left work, took less responsibility, and passed up promotions. Fatigue was reported by 96%, nausea by 88%, and anxiety by 62%. In 38% activities had to be given up and 60% reported that the adjuvant chemotherapy was a major disruptive factor in their lives. Despite this, 60% claimed they were glad to have participated and 75% that they would tell a friend to participate.

## Discussion

Adjuvant breast cancer trials have many variables that can affect comparability. These include selection, stratifications, design, treatment, and analysis.

Selection is one obvious critical factor. The staging systems used for selection in trials have not always been comparable. The majority of patients chosen for study have been operable, by conventional criteria, with positive nodes detectable by pathological examination. In terms of the UICC staging, this would include a mixture of stage II and III lesions. It would be helpful if all studies would use the TNM system and report selection with TNM terminology, since just saying stage II or III can be misleading. Stage I is generally not included, although it is in the Princess Margaret trial [19]. There does not appear to be a strong rationale for including stage I disease in adjuvant drug trials, although the prognostic impact of being ER− may change the view for that stage I subset.

In past trials, the local control therapy to which drug has been added has been relatively stable. It has consisted primarily of radical or modified radical mastectomy. It is generally considered that there is little prognostic difference, in terms of metastatic or local failure, between these two surgical procedures. The main variable in the local control baseline therapy has been postoperative radiation. Some studies, e.g., the Mayo Clinic study [1], have used this as a variable for randomization. Some studies, such as the NSABP and Milan protocols, have excluded it entirely. Many protocols in the United States allow it at the discretion of the investigator. These trials either stratify for radiation prior to randomization or do so in the ultimate analysis. Since Sternsjward [27] and Holland have stated that postoper-

ative radiation may increase metastatic failure due to immunosuppression, this may be dangerous. The radiation fields chosen may also be an important variable. Since the study by Host [15], many radiotherapists have begun to discuss the importance of treating the internal mammary nodes adequately, and this variable should be controlled for.

Future studies will be complicated by the various approaches to local control that are gaining in popularity. These include total mastectomy ± radiation, segmental resection ± radiation, and excisional biopsy plus radiation with an implant boost. If the local control therapy becomes more heterogeneous, as appears likely, it will greatly complicate the comparability analysis between studies.

Stratification is another aspect of adjuvant studies that must not be neglected. If a prognostic variable becomes potent enough, stratification for that variable extends to the design of separate studies based on that variable. This situation now obtains for menopausal status, and is beginning to be true for estrogen receptor site positivity in some groups. Where once a single study could be designed for a set of patients, we may now require four separate protocols for the same set. This will demand a greater input of patients if answers are to be obtained in a reasonable time frame.

Other prognostic variables that require stratification include: (1) degree of lymph node involvement; (2) clinical stage (tumor size); (3) possible pathologic factors, such as tumor necrosis. If local control therapy is not homogeneous that should be stratified for as well.

The drug treatments to be chosen have implicit variables, which are too numerous to enumerate except in superficial detail. There are six active drug classes to chose from, such as the alkylating agents (cyclophosphamide, phenylalanine mustard, thio-Tepa etc.), fluorinated pyrimidines, antifoles, vinca alkaloids, corticosteroids, and anthracyclines (adriamycin) [8]. The drug combinations that can be derived are many. The basis for choice up to the present has been activity in advanced disease. This is made difficult by the fact that there is no established combination derived from the six active drug classes that is clearly superior to many others reported in the literature [6, 9]. Significant variables would include the following: (1) adriamycin, yes or no; (2) corticosteroid, yes or no; (3) alkylating agent, yes or no. The regimens currently under adjuvant test reflect their variables: They include L-PAM, CMF, CFP, adriamycin and cytoxan, FAC, CMFP, L-PAM + 5-FU, and CMFVP. The common denominator in all combinations is an alkylating agent, either cyclophosphamide or L-PAM. There are few data that definitively indicate a choice between cyclophosphamide or L-PAM. Cyclophosphamide is more extensively studied in advanced disease, and has a platelet-sparing effect that makes it attractive for combination. On the other hand, it causes cystitis and alopecia, which can be disturbing. L-PAM can be more myelosuppressive and has a greater clinical history of carcinogenesis to put on the negative side of the ledger. It is unfortunate that a comparison between these two alkylating agents was not made earlier. The data from multiple myeloma indicate they are not totally cross-resistant, and few today would hold with the concept that an alkylating agent is an alkylating agent, is an alkylating agent....

The inclusion of adriamycin raises the spectre of cardiac toxicity. The endomyocardial biopsy experience at Stanford [5] has shown that all patients who receive a total dose in excess of 200 mg/m$^2$ have pathologic changes. Radiation to the mediastinum can enhance this and if radiation to the internal mammary nodes is critical, this could be an even more important factor. Nobody can foretell what will be the long-term impact of subclinical anthracycline cardiac damage. Since advanced disease studies do not show a dramatic advantage for adriamycin-containing combinations prudence might dicate avoiding this drug unless a compelling rationale can be brought forth.

Corticosteroids are still another variable. Some protocols use them on intermittent schedules, other on a more continuous basis. Their value in combination therapy is not fully established and at best they may give a 10%–15% higher response rate [6, 9]. They can have disturbing side effects. On the other hand, their adrenal-suppressing activity combined with the ovarian suppression potential of cytotoxic drug treatment might add another important wrinkle to the interpretation of final results.

Schedule is rarely given much emphasis in the design of adjuvant studies. A feature of most studies is the intermittent use of drugs. The rationale for this rests mainly on fear of continuous immunosuppression and data indicating that intermittent dosing allows for recovery of immunosuppression between cycles. There are no established experimental systems that are felt to predict for optimal schedule in the adjuvant situation, and so most schedules are empirical derivations from what has been used in the advanced metastatic state.

Duration is another unknown factor. The early adjuvant studies with thio-Tepa and 5-FU [12] used only a single course, as their rationale was to attack circulating tumor cells. The current hypothesis of attacking metastatic foci calls for longer treatment, based on the implications of the cell kill hypothesis and the rodent transplantable tumor models. The major trials treat for 1 year, 18 months, 2 years, or longer. The choice of duration is strictly empirical. It is hard to understand why one course of thio-Tepa could exert a positive effect on premenopausal women with four or more positive nodes while phenylalanine mustard for 18 months did not. The

equation must also take in Nissen-Meyer's positive results with one course of cyclophosphamide. It is easier to reconcile this contradiction by postulating a hormonal effect for the drugs rather than a classic cell kill effect. Currently, Bonadonna is testing six against twelve courses of CMF for premenopausal patients, and this is the only trial that attempts to look at duration in any meaningful way.

Intensity of therapy is still another variable worthy of debate. The cell kill hypothesis implies that with increasing doses of an effective regimen, greater percentages of cells will be killed and zero cells will be achieved more rapidly. In advanced disease, this has translated to drugs being given at their maximally tolerated dose and some level of toxicity being considered a sine qua non of an effective dose. In adjuvant trials, there has been concern that toxicity would be poorly tolerated by women and that any drug-related mortality would be unacceptable in a potentially cured patient. Therefore, the dose levels chosen have tended to be somewhat lower than have been given in advanced disease. It may be that these lowered dose levels are not effective enough, in terms of cell kill, to give the desired cure. More intense therapy may need to be given. The mathematical model hypothesis of Norton and Simon [24] indicates that the most sensitive phase in the growth curve is not when the tumor cell burden is lowest but at the 37% growth point on the Gompertz curve. This indicates a need for late intensification in adjuvant trials or higher doses given initially, depending on what the residual tumor cell burden is postulated to be. In postmenopausal women, Bonadonna is testing a kind of late intensification in which the same total dose of drug is given in two groups but in one lower doses are used in the beginning and higher doses in the final cycles. Whether this is a true test of the Norton-Simon hypothesis and whether the entire hypothesis is ready for a clinical test is open to question.

Design considerations are of extreme importance and center predominantly around the raging debate about prospectively randomized studies as against those with historical controls. This debate is too extensive to go into in this paper, but a few points are worth emphasizing. Adjuvant chemotherapy in breast cancer, if generally accepted, would constitute a major change in treatment policy, with resultant economic and psychosocial impact. It is clear from the data to date that a penicillin-like magic bullet effect is not likely. The benefits reported in premenopausal women are significant and of potential widespread benefit, but are not so dramatic that the scientific security of a prospectively designed controlled trial can be foregone. The end point of these trials is not complete remission but relapse-free survival, and large numbers are required to account for all the variables. The disease is highly heterogeneous and the possible sources of bias are many. The discovery of the estrogen receptor site is a good example of a new prognostic variable that has been found, and only randomization offers a reasonable possibility that such hidden variables might come out, even in two treatment groups.

Another design consideration is what constitutes an appropriate control group in newly designed adjuvant studies. A clinical trial should be based on the data from earlier studies. It should compare the best standard treatment with something it is hoped will be superior. According to this criterion, the appropriate reference preparation for use in premenopausal women with one to three positive nodes is either L-PAM or CMF. With four or more nodes in premenopausal women, it is CMF. If one wanted to be difficult, one could also propose that one perioperative course of thio-Tepa is also an appropriate control for this subset. In postmenopausal women, a surgery-only control seems more than appropriate, since L-PAM, CMF, and all other regimens have been shown to be of no benefit in this large subgroup. Trials with this control of surgery only have been started by the Eastern Cooperative Oncology Group (P. Carbone, personal communication).

Analysis of the data is one more consideration of importance. The short-term analysis involves a comparison of relapse-free survival against the acute toxicity cost. Relapse-free survival is reported according to actuarial techniques. It is clear from both the L-PAM and CMF studies that the actuarial projection at a median follow-up time of around 18 months was not confirmed at a median follow-up time of 3 or 4 years. At any point in time, a projected actuarial curve can either stay the same or deteriorate. Each relapse, assuming no new entries, will cause the curve to fall. Consideration needs to be given to determining what is the earliest possible time an actuarial projection of relapse-free survival can be made with reasonable confidence in its prediction of the ultimate true outcome.

The final analysis of adjuvant studies in breast cancer will be a long-term proposition requiring 10 years or more of follow-up. The final end point will be survival. Survival will be complicated by the therapy given after relapse if it occurs. It is possible that adjuvant chemotherapy could shorten survival after a relapse, because of refractoriness to secondary drug treatment. This possibility demands that overall survival be looked at as the final point. A regimen that enhanced relapse-free survival but not overall survival would be of some interest, but of much diminished overall value. The cost-benefit ratio in adjuvant trials demands that second tumors be analyzed as well as chronic toxicity. In patients treated with adjuvant adriamycin mortality due to cardiac failure should be analyzed for in relation to a non-adriamycin-containing control group. An increase in second tu-

mors has been reported with long-term L-PAM in multiple myeloma and ovarian cancer, chlorambucil in breast cancer, and MOPP plus radiation in Hodgkin's disease. This is still another factor that can affect overall survival as compared to relapse-free survival.

## Conclusion

*Where should adjuvant chemotherapy be used routinely, if at all?*

I do not feel that adjuvant chemotherapy has been clearly established as having definitive value. Only two studies, with proper surgery-only control groups, have follow-up in excess of 3 or 4 years. At this moment the L-PAM study appears to show diminished recurrence rates for premenopausal women with one to three positive nodes. The CMF study has similar results for all premenopausal women, regardless of the amount of nodal involvement. These results are positive and encouraging, but a long way from establishing absolute value. At this moment there are no data to support the use of adjuvant chemotherapy routinely for post menopausal women; both L-PAM and CMF have had minimal impacts for this large subset of women.

In the short term, the cost-benefit ration analysis for adjuvant chemotherapy studies in breast cancer will be relapse-free survival versus acute toxicity. According to short-term analysis criteria, adjuvant chemotherapy appears to benefit premenopausal women with positive nodes. The long-term analysis will be overall survival against chronic toxicity. Chronic toxicity will include organ damage, e.g., adriamycin cardiac toxicity and the induction of second tumors. According to long-term analysis criteria, the value of adjuvant chemotherapy has not yet been established. Despite this, I think drugs should be given to premenopausal women with positive nodes, on the basis of the great likelihood that the short-term analysis will predict for the long-term analysis. I do have a strong feeling that the long-term analysis will give a result that is not as positive as the current short-term analysis indicates, albeit positive overall.

If chemotherapy is to be given routinely to premenopausal women, it should be CMF, especially for women with four or more positive nodes. No other drug regimen has been shown against a surgery-only control to diminish recurrence rates with a reasonable follow-up time. The use of adriamycin-containing regimens should be discouraged for routine use, since the long-term cardiac toxicity risk has not been established.

There is no indication for the use of chemotherapy routinely for node-negative women. There is also no indication for the routine use of immunotherapy either alone or with chemotherapy in any situation.

*How should adjuvant chemotherapy research proceed?*

The essential aspect of adjuvant drug research in breast cancer has to be a recognition that the clinical experiment will be a long-term experiment requiring a significant number of patients to ensure comparability for the many critical variables. Stratification variables that should be taken account of include pathologic lymph node status, menopausal status, clinical stage, and estrogen receptor status. The best-risk patient would appear to be postmenopausal, in clinical stage I, lymph node-negative and ER+. The poorest prognosis appears to be that of a woman who is premenopausal and in clinical stage II, has more than four positive nodes, and is ER−. Clinical studies should embrace large enough numbers to account for all these variables.

Past experience has taught us that actuarial analysis with a median follow-up of 12–24 months can be misleading. While interim analysis of clinical trials are essential, although occasionally misleading, there should be a minimum time established before major publication is contemplated. This probably should be at least 3 years.

The use of historical controls should be approached with great caution. The discovery of the prognostic importance of the hormone receptors is an excellent example of how new variables can be discovered. It will be extremely difficult to compare any study group that includes the ER data with any historical control group that does not. Where historical controls are used great caution should be used in interpretation of the $P$ values. With proper randomization, a $P$ value of 0.05 may well imply biological significance, but with historical controls it may be that even a $P$ value of 0.001 does not imply biological significance. It should also be remembered that the historical control always has a longer follow-up time than the study group, and that in time more relapses and deaths can usually be expected.

A very sticky problem is the definition of what constitutes a proper control group for postmenopausal women in adjuvant trials. In my opinion, a surgery-only control group is both appropriate and ethical. Studies that use either L-PAM or CMF as controls are using regimens not shown to be effective when compared with surgery only. Granted that relapse rates have not been increased by these regimen or survival shortened, there are still the factors of physical morbidity (acute toxicity), psychosocial morbidity, and economic morbidity. Studies that use regimens other than L-PAM or CMF as 'controls' are using regimens that have been proven neither effective or safe. The use of prior surgery-only groups as 'historical controls' is of debatable value.

Approaches that can be considered for trial include the following:

1. More intensive use of the six active drugs; a) Higher doses; b) Late intensification; c) Greater number of drugs; d) Longer duration
2. Drugs plus hormones
3. Drugs plus immunotherapy
4. Drugs plus radiation
5. New drugs
6. Preoperative chemotherapy

One of the critical questions in the design of protocols is what level of stratification to impose for the development of separate protocols. For pathologic stage II disease one could prepare separate protocols for the following subjects:

1. Premenopausal vs. postmenopausal
2. ER+ vs. ER−
3. 1–3 +ve nodes vs. 4 +ve nodes

Several groups are now undertaking separate studies for premenopausal and postmenopausal women, with the impact of the prognostic value of the ER assay and the possibility that this too may have to be included as a protocol-separating variable. The possible complexities for protocol design are outlined below in the following examples:

I. Premenopausal ER−

R → Chemotherapy A
R → Chemotherapy B

II. Premenopausal ER+

R → Chemotherapy A
R → Oophorectomy
R → Chemotherapy + oophorectomy

III. Postmenopausal ER−

R → Chemotherapy A
R → Control (surgery only)

IV. Postmenopausal Er+

R → Tamoxifen
R → Chemotherapy A + tamoxifen
R → Control

Obviously these are only some of the possibilities for broad arms to choose from, ignoring the variables of drug choice, schedule, duration, intensity, etc.

## References


1. Ahmann, D. L., Scanlon, P. W., Bisel, H. F. et al.: Repeated adjuvant chemotherapy with phenylalanine mustard as 5-fluorouracil, cyclophosphamide and prednisone, with or without radiation after mastectomy for breast cancer. Lancet **1978 II,** 893–896
2. Bonadonna, G., Brusamolino, E., Valagussa, P., Rossi, A., Brugnatelli, L., Brambilla, C., DeLena, M., Tancini, G., Bajetta, E., Musumeci, R., Veronesi, U.: Combination chemotherapy as an adjuvant treatment in operable breast cancer. N. Engl. J. Med. **294,** 405–410 (1976)
3. Bonadonna, G., Rossi, A., Valagussa, P., Banfi, A., Veronesi, U.: Adjuvant chemotherapy with CMF in breast cancer with positive nodes. In: Adjuvant therapy of cancer. Salmon, S. E., Jones, S. E. (eds.), pp. 83–94. Amsterdam: Elsevier/North Holland Biomedical Press 1977
4. Bonadonna, G., Valagussa, P., Rossi, A., Veronesi, U.: Improvement of disease-free and overall survival by adjuvant CMF in operable breast cancer. Proc. Am. Assoc. Cancer Res. **19,** 215 (1978)
5. Bristow, M. R., Mason, J. W., Billingham, M. E., Daniels, J. R.: Doxorubicin cardiomyopathy: Evaluation by phonocardography, endomyocardial biopsy, and cardiac catheterization. Ann. Intern. Med. **88,** 168–175 (1978)
6. Broder, L. E., Tormey, D. C.: Combination chemotherapy of carcinoma of the breast. Cancer Treat. Rev. **1,** 183–203 (1974)
7. Buzdar, A. V., Gutterman, J. U., Blumenschein, G. R. et al.: Intensive postoperative chemoimmunotherapy for patients with stage II, stage III breast cancer. Cancer **41,** 1064–1075 (1978)
8. Carter, S. K.: The chemical therapy of breast cancer. Semin. Oncol. **1,** 131–144 (1974)
9. Carter, S. K.: Integration of chemotherapy into combined modality treatment of solid tumors. VII. Adenocarcinoma of the breast. Cancer Treat. Rev. **3,** 141–174 (1976)
10. Cole, M.: Prophylactic compared with therapeutic X-ray artificial menopause. In: Second tenovus workshop on breast cancer. Joslin, C. A. F., Gleave, E. N. (eds.). Cardiff: Tenovus 1970
11. Davis, T. E., Rose, D. P.: Effect of adjuvant chemotherapy on endocrine function in breast cancer. Proc. Am. Assoc. Cancer Res. **18,** 49 (1977)
12. Fisher, B., Ravdin, R. G., Ausman, R. K. et al.: Surgical adjuvant chemotherapy in cancer of the breast. Results of a decade of cooperative investigation. Ann. Surg. **168,** 337–356 (1968)
13. Fisher, B., Carbone, P., Economou, S. G. et al.: L-Phenylalanine mustard (L-PAM) in the management of primary breast cancer. A report of early findings. N. Engl. J. Med. **292,** 117–122 (1975)
14. Fisher, B., Redmond, C. et al.: Studies of the National Surgical Adjuvant Breast Project (NSABP). In: Adjuvant therapy of cancer. Salmon, S. E., Jones, S. E. (eds.), pp. 67–68. Amsterdam: Elsevier/North Holland Biomedical Press 1977
15. Host, H., Brennhovd, I. O.: The effect of post-operative radiotherapy in breast cancer. Int. J. Radiat. Oncol. Biol. Phys. **2,** 1061–1067 (1977)
16. Knight, W. A., Livingston, R. B., McGuire, W. L.: Absent estrogen receptor and decreased survival in breast cancer. Cancer Res. **37,** 4674–4677 (1977)
17. Knight, W. A., Livingston, R. B., Gregory, E. J. et al.: Absent estrogen receptor and decreased survival in human breast cancer. Proc. Am. Assoc. Cancer Res. **19,** 392 (1978)
18. Livingston, R. B., Hart, J. S.: The clinical applications of cell kinetics in cancer therapy. Annu. Rev. Pharmacol. Toxicol. **17,** 529–543 (1977)
19. Meakin, J. W., Allt, W. E. C., Beale, F. A., Brown, T. C., Bush, R. S., Clark, R. M., Fitzpatrick, P. J., Hawkins, N. V., Jenkin, R. D. T., Pringle, J. F., Rider, W. D., Hayward, J. L., Bulbrook, R. D.: Ovarian irradiation and prednisone following surgery for carcinoma of the Breast. In: Adjuvant therapy of cancer. Salmon, S. E., Jones, S. E. (eds.), pp. 95–100. Amsterdam: Elsevier/North Holland Biomedical Press 1977
20. Meyer, J. S., Bauer, W. C.: Thymidine labeling index of human breast carcinoma. In: First annual meeting of cell kinetics society (abstract), p. 45. Birmingham, Alabama: 1977.
21. Meyerowitz, B., Sparks, F. C., Spears, I. K.: Psychosocial aspects of adjuvant chemotherapy for breast cancer. Proc. Am. Assoc. Cancer Re. **19,** 359 (1978)

22. Nevinny, H. B., Nevinny, D., Rosoff, C. B. et al.: Prophylactic oophorectomy in breast cancer therapy – Preliminary report. Am. J. Surg. **117,** 531 (1969)
23. Nissen Meyer, R.: The role of prophylactic castration on the therapy of human mammary cancer. Eur. J. Cancer **3,** 395 (1967)
24. Norton, L., Simon, R.: Tumor size, sensitivity to therapy and the desing of treatment scheduled. Cancer Treat. Rep. (In press, 1978)
25. Ravdin, R. G., Lewison, E. F., Slack, N. H. et al.: Results of a clinical trial concerning the worth of prophylactic oophorectomy for breast cancer. Gynecol. Obstet. **131,** 1055 (1970)
26. Rose, D. P., Davis, T. E.: Ovarian function in patients receiving adjuvant chemotherapy for breast cancer. Lancet **1977 I,** 1174–1176
27. Stjernsward, J.: Decreased survival related to irradiation postoperatively in early breast cancer. Lancet **1974 II,** 1285
28. Wendt, A. G., Chase, E. M., Miller, R. C. et al.: Adjuvant treatment of breast cancer with adriamycin-cyclophospamide ± radiotherapy. Proc. Am. Assoc. Cancer Res. **19,** 392 (1978)

Received July 24, 1978/Accepted September 1, 1978