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# Twenty-four Hour Combination Chemotherapy: a Feasibility Study with Implications for Improved Adjuvant Treatment of Breast Cancer

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**Abstract**—*Forty-three patients with metastatic breast cancer were treated with a total of 385 cycles of combination chemotherapy consisting of adriamycin, cyclophosphamide, 5-fluorouracil, methotrexate and vincristine sulphate given over 24 hr and followed by a leucovorin 'rescue'. Thirty patients (70%) responded with three complete remissions. Thirteen patients did not respond, including six in whom the progression of disease was apparently arrested. Duration of response ranged from 2 to 24 months. At 20 months, 10 of 30 responding patients were alive compared with 1 of 13 non-responders. Toxicity was minimal apart from nausea and vomiting. This study confirms previous reports that intensive chemotherapy can be given safely over 24 hr without loss of therapeutic effect. This regimen is now being tested as an adjuvant to mastectomy in node-positive operable breast cancer.*

## INTRODUCTION

THE PIONEERING work of Greenspan [1] established that combination chemotherapy can produce a high response rate in women with metastatic breast cancer and this has now become an accepted form of treatment for patients with advanced disease. In 1976 Bonadonna *et al.* [2] published preliminary results from a controlled trial of combination chemotherapy using cyclophosphamide, methotrexate and 5-fluorouracil as an adjunct to surgery in histologically node-positive operable breast cancer, suggesting that this form of treatment might have the potential to cure more patients. At this time it became clear that adriamycin was probably the single most effective agent in breast cancer [3] and should be tested in combination with other drugs in an adjuvant role. We have already shown that the administration of cyclophosphamide, 5-fluorouracil, methotrexate and vincristine given over 24 hr to patients with miscellaneous solid tumours [4] and breast cancer [5] was far less toxic, and without loss of therapeutic effect, than the more usual approach of administering drugs over several days (cited in [6]). Accordingly, using the same experimentally based approach, we decided in 1976 to carry out a feasibility study, integrating adriamycin with our original four-drug protocol in patients with metastatic breast cancer. This paper describes the results of that study and this protocol is now being used as an adjuvant to mastectomy in a randomised, prospective, controlled trial by the West Midlands Oncology Association Breast Cancer Study Group.

## MATERIALS AND METHODS

Forty-three patients with disseminated breast cancer were given a total of 385 cycles of combination chemotherapy, as scheduled in Fig. 1. Fixed rather than size-adjusted dosage was used, based on results from our previous studies [4, 5] and kinetic [7] and pharmacologic considerations. Over 24 hr the toxicity of class II drugs, i.e. methotrexate and vincristine, is not dose-dependent, but the doses of the class III drugs, i.e. cyclophosphamide, adriamycin and 5-fluorouracil, were reduced proportionately because in combination they are additively toxic to the bone marrow. Treatment cycles were repeated every three weeks. In responding patients the inter-treatment interval was sometimes extended to 4–6

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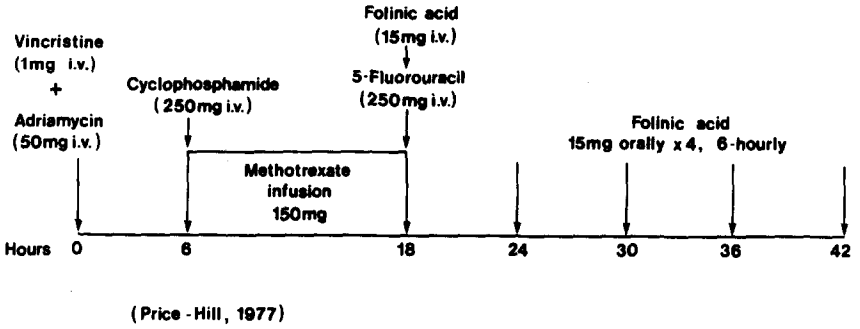


*Fig. 1. Chemotherapy protocol.*

weeks. The following precautions were observed in all patients:

1. In the presence of a lowered peripheral blood count, treatment was delayed until the count had returned to its original level.
2. As methotrexate is excreted in the urine, care was taken that all patients were adequately hydrated with a good urine output during drug administration (at least 2 l of urine in 24 hr). Extended leucovorin 'rescue' (three times longer than normal) was afforded to patients with evidence of impaired renal function. A creatinine clearance of less than 60 ml/min was taken as an absolute contra-indication to therapy.
3. Doses of cyclophosphamide, adriamycin and 5-fluorouracil were halved in patients who had received extensive thoracic, pelvic or abdominal irradiation.
4. Patients with a history of cardiac failure were excluded from the study. The total dose of adriamycin never exceeded 550 mg/m$^2$, and the dose was halved in patients with impaired liver function.
5. Vincristine was withdrawn if neurotoxicity developed.

Response was assessed using UICC criteria [8]. A complete response (CR) was defined as the disappearance of all clinical evidence of disease. Partial response (PR) required a decrease of greater than 50% in the product of two perpendicular diameters of all measurable lesions. Disease arrest was counted as a non-response.

## RESULTS

Of 43 patients, 30 (70%) responded to chemotherapy. Twenty-seven were partial responders and 3 achieved a complete response. No response occurred in 13 patients (including 6 with disease arrest).

Patient characteristics are detailed in Table 1. Chemotherapy responders had better survival figures: at 20 months 11 of 30 responding patients were alive compared with 1 of 13 non-responders.

Serious side-effects were minimal. Alopecia occurred in all 43 patients and wigs were required, but 19 patients had no other side-effects. Nausea and vomiting were the most troublesome symptoms and occurred in approximately one-third of treatment cycles. There was little haematologic toxicity. Out of 385 courses of treatment, a haemoglobin of less than 9 g/dl was recorded on eight occasions — these patients were transfused. The total white blood cell count fell below 2000 on 2 occasions and the platelet count below 100,000 on 10 occasions. In 4 patients the platelet count fell to below 70,000/mm$^3$, but in

*Table 1. Characteristics of 43 patients*

| | Chemotherapy responders (30) | Chemotherapy non-responders (13) |
|---|---|---|
| Age: | | |
| average | 52 | 56 |
| range | 35–69 | 41–74 |
| Menopausal status: | | |
| pre-menopausal | 7 | 2 |
| peri-menopausal | 4 | 2 |
| post-menopausal | 18 | 9 |
| patient had bilateral oophorectomy | 1 | — |
| Site of first recurrence: | | |
| bone | 6 | 2 |
| soft tissue | 9 | 7 |
| visceral | 13 | 2 |
| bone and visceral | 2 | 2 |
| Duration of response: | | |
| mean | 11 months | — |
| median | 10 months | — |
| Survival: | | |
| mean | 19.5 months | 13 months |
| median | 17 months | 6 months |
| No. of patients alive | 3 at 14, 26 and 50 months | 1 at 49 months |
| Patients lost to follow-up | 1 at 8 months | 0 |

these patients this represented a fall of only 40% of their normal baseline level, which was low before treatment started. Drug treatment was delayed for 1 week on 3 occasions and for 2 weeks twice. On no occasion was myelosuppression sufficient to produce infections or to require supportive measures. Other toxicities are summarised in Table 2.

*Table 2. Side-effects from 385 chemotherapy treatment cycles*

| | |
|---|---|
| Cystitis | 1 |
| Diarrhoea | 1 |
| Nausea and vomiting | 130 |
| Peripheral neuropathy | 1 |
| Mucositis | 0 |
| Cardio-toxicity | 0 |
| Deaths | 0 |

## DISCUSSION

Any chemotherapy regimen under consideration for use as an adjunct to surgery for breast cancer must fulfil two requirements. Firstly, it should be effective in advanced disease and secondly, it must be safe. The therapeutic effect of the protocol described in this report compares favourably in terms of objective response with other chemotherapeutic regimens in current use [9]. This study confirms our previous findings [4, 5, 10] that intensive combination chemotherapy can be given safely without loss of therapeutic effect by giving anti-tumour drugs over 24 hr as opposed to several days. No severe myelosuppression occurred, and apart from nausea, vomiting and alopecia, other toxic effects were minimal. Although treatment involved an overnight stay in hospital every 3 weeks, patient compliance has been good, and full dosage of chemotherapy can therefore be reliably administered. In addition, admission to hospital allows for effective control of nausea and vomiting and reduction of hair loss by scalp-cooling techniques. The addition of adriamycin to the four drugs used in our earlier studies [4, 5] in this small number of patients does not appear to have altered the response rate significantly (66% versus 70%), but it does seem to have increased the median duration of response from 5½ to 10 months and the median survival time from 9 to 17 months. This would tend to agree with other reports of the benefit of using adriamycin-containing regimens for treating breast cancer (cited in [11]).

Experimental [12, 13], theoretical [14] and clinical studies [15, 16] suggest that adjuvant chemotherapy may only achieve maximum effect if given intensively in a maximally tolerated dose beginning as soon as possible after surgery. Recent results [17] published since this present study was started suggest that the addition of tamoxifen might further improve the results of adjuvant chemotherapy. The chemotherapy protocol described here is currently under test in a prospective, randomised, controlled trial in the West Midlands. Although it is too early to report therapeutic effect, the safety and acceptability of the schedule has been confirmed [18].

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