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Delayed Recovery of Peripheral Blood Cell Numbers after Adjuvant Cytotoxic Chemotherapy for Stage II Breast Cancer

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Summary. *A study was made on the recovery of the bone marrow after adjuvant chemotherapy given to 30 post-mastectomy patients with stage II breast cancer treated with either melphalan or melphalan and methotrexate at 6-weekly intervals for 1 year. Counts of peripheral blood cells were made serially during treatment and then for a further 2 years after stopping chemotherapy. Mean counts for all cell types fell during chemotherapy and recovery was long-delayed. Thus 24 months after chemotherapy, mean counts for total leucocytes and platelets were significantly lower than mean pretreatment counts and counts for a normal female population, and the count for neutrophils was significantly lower than the count before treatment; after 24 months mean counts for lymphocytes were not significantly depressed. Melphalan was assumed to be the agent responsible. Slow haematological recovery after cessation of adjuvant chemotherapy with one particular regimen points to the need for including long-term post-chemotherapy observation of the bone marrow in the assessment of adjuvant chemotherapy programmes.*

Introduction

Cytotoxic chemotherapy for breast cancer, based on the premise that micrometastases are susceptible to such treatment, prolongs the disease-free interval and may improve survival, particularly in pre-menopausal patients [2]. Initial success was reported with melphalan [6], and later with combinations of drugs, e. g., cyclophosphamide, methotrexate, and 5-fluorouracil [2]; the toxicity of these drugs is considered to be acceptable in view of the improved results and the reversibility of the side-effects [2]. In a trial of adjuvant cytotoxic chemotherapy with melphalan for stage II breast cancer, routine haematological observations were continued for up to 2 years after the 1-year period of treatment. This study presents the pattern of haemopoietic and lymphopoietic recovery after cytotoxic chemotherapy.

Patients and Methods

Patients. Thirty-four women with breast cancer with histological evidence of axillary node metastases at the time of mastectomy were entered, with their informed consent, into a randomized adjuvant chemotherapy trial in which melphalan was compared with melphalan and methotrexate. Patients were entered into the trial after mastectomy when results of histological examination of axillary lymph nodes were known. The protocol did not include studies before mastectomy was performed, and the interval between mastectomy and entry into the study was 2–4 weeks. There were four early exclusions, and the remaining 30 patients constituted the study population. One group (14 patients) received melphalan 0.15 mg per kg, later increased to up to 0.2 mg per kg for days 1–6 of each cycle (total dose 0.9–1.0 mg per kg), and the other group (16 patients) received melphalan together with methotrexate 0.2 mg per kg on day 8 of each cycle. Treatment cycles were repeated 6-weekly for 1 year, and doses of drugs were adjusted according to test results. Observations were made for 2 years after the 1-year period of treatment. If there were recurrences of cancer, patients were withdrawn from the study population but remained under observation in the clinic; there were 12 such withdrawals over the 3-year period of study.

Methods. The patients were studied at 3-monthly intervals according to a protocol which included peripheral blood counts, together with tests of humoral and cell-mediated immunity according to a previously described schedule [14]. The present report is limited to the results of the haematological studies. Venous blood was collected between 08.00 and 13.00 h. White cell counts were performed on a Coulter-S counter, differential counts were performed manually on stained smears, and platelets were

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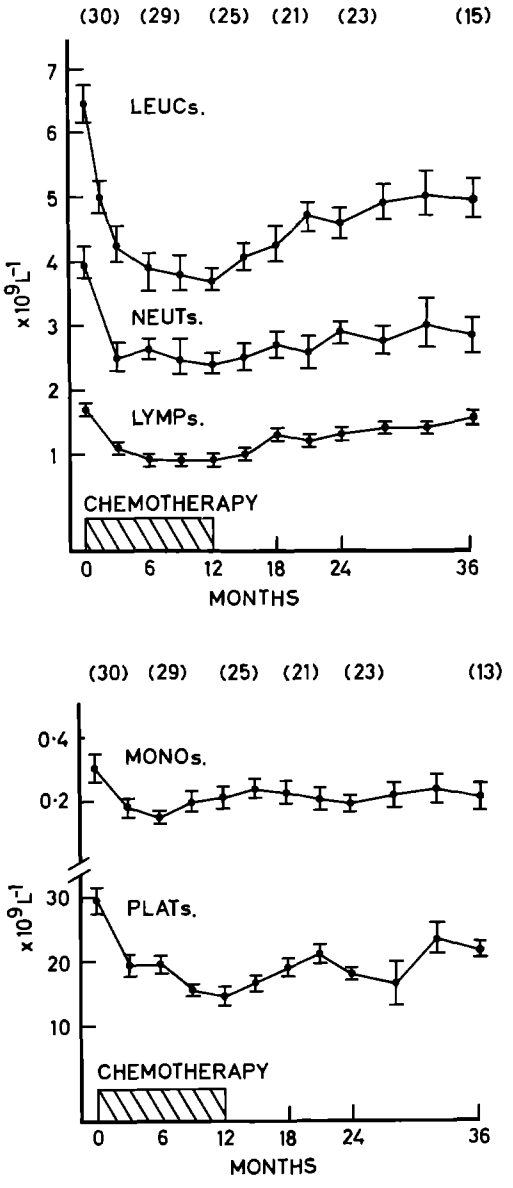

Fig. 1. Serial counts (geometric means ± standard error) *(above)* of total leucocytes (leuc), neutrophils (neut) and lymphocytes (lymp), and *(below)* of monocytes (mono) and platelets (plat) in patients (numbers in parentheses at top) whilst receiving adjuvant chemotherapy and 2 years thereafter. Statistical analyses are shown in Table 1

counted on a thrombocounter (Coulter Electronics, GB). Normal values are those cited for women in the morning [1, 3].

Statistics. There is a log-normal distribution of total and differential white cell counts [1] and, probably, platelet counts [3]. Hence geometric means were calculated from log-transformed data. Differences between groups were tested for significance by Student's *t*-test. Values for a normal population were derived from the report of Bain and England [1] for leucocytes, lymphocytes, and monocytes, using the figures cited for women in the morning, and the report of Brecher and Cronkite [3] for platelets.

Results

Peripheral blood cell counts for leucocytes, neutrophils, lymphocytes, monocytes, and platelets for the two groups of patients, those treated with melphalan and those treated with melphalan and methotrexate, were found not to differ significantly at any time, and hence data for the two groups were combined. Figure 1 and Table 1 show the results for cell counts during chemotherapy and for 2 years thereafter, with results for statistical comparisons between all post-chemotherapy counts and initial counts, and counts for a normal population.

The pre-chemotherapy counts for the study population did not differ significantly from those of the normal population, except for a lower mean number of monocytes. During the first 6 months after chemotherapy was begun the mean counts for all blood cell types fell progressively; after chemotherapy was ceased the mean counts increased, but did not reach pretreatment levels. Thus at 36 month mean counts for total leucocytes and platelets remained significantly lower than mean counts before treatment and mean counts for the normal population, and for neutrophils the mean counts were significantly lower than mean counts before treatment. Up to 24 months, but not at 36 months, lymphocyte counts were significantly lower than mean counts before treatment and mean counts for the normal population.

Discussion

The present report describes prolonged depression, for up to 3 years, of haemopoiesis and lymphopoiesis in 30 women with stage II breast cancer treated by mastectomy followed by adjuvant chemotherapy for 1 year. The drugs used were melphalan in 14 patients and melphalan with methotrexate in 16 patients and, since there was no difference between the groups treated with or without methotrexate, the major effects were presumably those of melphalan. Recovery, albeit slow, could eventually be complete, as judged by trends up to 2 years after treatment was stopped. Depression of haemopoiesis and lymphopoiesis is a well-recognized accompaniment of treatment with radiation and with immunosuppressive and cytotoxic drugs [13], and this can be prolonged after radiotherapy [12]. In the mouse, residual marrow damage after exposure to certain cytotoxic drugs, particularly alkylating agents, is well established [10], but in man delayed recovery of haemopoiesis after cytotoxic drugs is less well documented [4, 9]. Lohrmann et al. [9] reported depressed granulopoie-

Table 1. Mean counts (standard error of mean) for blood cells for normal populations (1, 3) and patients with stage II breast cancer given adjuvant chemotherapy for 1 year

Times	Cell counts[a]				
	Leucocytes	Neutrophils	Lymphocytes	Monocytes	Platelets
Normals	5,665 (170)	2,952 (80)	1,956 (60)	433 (15)	248 (10)
Pre-chemotherapy	6,450 (310)	3,980 (260)	1,738 (124)	302 (46)	295 (20)
12 months	3,700 (200)[1]	2,400 (160)[1]	891 (86)[1]	209 (36)[1]	145 (14)[1]
24 months	4,570 (240)[1]	2,880 (170)[2]	1,318 (127)[1]	191 (27)[1]	178 (12)[1]
36 months	4,898 (350)[1]	2,818 (531)[2]	1,549 (111)[4]	207 (40)[3]	214 (15)[1]

[a] Counts $\times 10^{-6}$ per litre, platelets $\times 10^{-3}$ per litre
[1] Significantly lower ($P < 0.05$) than mean pre-chemotherapy counts and mean counts for normal population
[2] $P < 0.05$ for mean pre-chemotherapy counts and $0.1 > P > 0.05$ for mean counts for normal population
[3] $0.1 > P > 0.05$ for mean pre-chemotherapy counts and $P < 0.05$ for mean counts for normal population
[4] $P > 0.1$ for mean chemotherapy counts and $0.1 > P > 0.05$ for mean counts for normal population

sis for more than 200 days after adjuvant chemotherapy, whereas in the present study recovery was incomplete even after 2 years. Whilst melphalan was considered to be the agent causing post-chemotherapeutic depression of the bone marrow in the present study, this may also occur with various other regimens, e. g., adriamycin and cyclophosphamide, as reported by Lohrmann et al. [9].

The significance of these prolonged effects of adjuvant chemotherapy on blood cell numbers is uncertain. Studies in the mouse [10] suggest that there is depletion at the stem cell level of a proliferating cell compartment, with marrow reserves becoming limited and sensitivity increasing to subsequent exposures to myelosuppressive agents. Further information might have been obtained in the present study from examination of the bone marrow by means of morphology and measurement of colony-forming cells, but since there was no symptomatic depression of the bone marrow this was not undertaken. From the present observations, there seems to be a need to compare the bone marrow tolerance of women who relapse in adjuvant trials and are then given further chemotherapy with that of previously untreated patients. A further issue is that of secondary carcinogenesis, for which there is increasing evidence after use of immunosuppressive or cytotoxic drug therapy [11] and, even at this relatively early phase of adjuvant chemotherapy, there is already one report of an increased incidence of leukaemia after treatment with chlorambucil for breast cancer [8]. Although the International Agency for Research on Cancer cites melphalan as the only cytotoxic drug definitely regarded as carcinogenic [7], other cytotoxic drugs may well have this potential.

Our present findings of slow recovery of peripheral blood cell numbers after adjuvant cytotoxic chemotherapy need to be weighed against known and potential gains as the practice of adjuvant chemotherapy of cancer becomes progressively extended and, in particular, to earlier stages of disease such as stage I breast cancer where the expectation of remaining disease-free for 10 years after surgery is relatively high, 76% [5]. In any event, observation of haematological function after cessation of adjuvant chemotherapy could be recommended to ascertain which regimens carry the risk of causing prolonged suppression of the bone marrow.

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