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The Influence of Adjuvant Chemotherapy on Outcome after Relapse for Patients with Breast Cancer

S.J. Houston, M.A. Richards, A.E. Bentley, P. Smith and R.D. Rubens

This study examines the outcome following relapse for 176 patients who had been entered into a randomised trial comparing adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with no adjuvant therapy (controls). Relapse has occurred in 65/144 (45%) of the CMF group and 111/158 (70%) of controls ($P < 0.0001$). 123/176 patients received endocrine treatment after relapse with higher response rates (38 vs. 18%, $P < 0.05$) and longer time to progression (23 vs. 19 weeks, $P = 0.03$) for controls. 94/176 received chemotherapy after relapse again with higher response rates (47 vs. 23%, $P = 0.05$) and longer time to progression (17 vs. 9 weeks, $P = 0.03$) for controls. Despite this, survival after relapse was the same for the two groups (median 16 months). However, on subgroup analysis, postmenopausal patients who had received adjuvant CMF had shorter survival ($P = 0.03$). These results suggest that prior adjuvant therapy should be a stratification factor in clinical trials in advanced disease.
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INTRODUCTION

THE OVERVIEW analysis conducted by the Early Breast Cancer Trialists Collaborative Group [1] has demonstrated beyond reasonable doubt that adjuvant chemotherapy prolongs survival, particularly for women under the age of 50 years. Despite this, relapse after adjuvant chemotherapy remains a significant problem. It is clearly important to know whether prior treatment with adjuvant chemotherapy compromises response and survival in patients who suffer a recurrence of their disease. Published reports show conflicting results with some showing an adverse effect of prior adjuvant chemotherapy [2–4] and others apparently showing no such effect [5–7].

This report analyses factors influencing survival after relapse for 176 patients treated at Guy's Hospital in the Guy's/Manchester trial [8]. In that study patients with positive axillary lymph nodes were randomised to receive cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) for a period of 12 months or no adjuvant chemotherapy (control) following modified radical mastectomy or breast conservation including full axillary clearance. A recent update of outcome in that trial showed a significant benefit in relapse-free survival and survival for patients treated with CMF. This benefit was confined to premenopausal patients [9]. In this paper, time to relapse, survival after relapse, response to endocrine therapy and response to chemotherapy for patients in the two arms of the study have been compared.

PATIENTS AND METHODS

A total of 312 patients under the age of 65 years with operable breast cancer and histologically proven axillary node involvement managed at Guy's Hospital between October 1979 and December 1985 were entered into the Guy's/Manchester trial comparing CMF with no adjuvant therapy. Between October 1979 and October 1981 primary treatment for all patients was modified radical mastectomy. From October 1981 onwards patients with tumours less than 4 cm in diameter

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underwent either modified radical mastectomy or a breast conserving treatment programme comprising tumorectomy, axillary clearance, interstitial iridium treatment and external beam radiotherapy as part of a further randomised study (EORTC 10801). 146 of the 312 patients received adjuvant CMF (cyclophosphamide 80 mg/m^2 given orally on days 1–14; methotrexate 32 mg/m^2 and 5-fluorouracil 480 mg/m^2 given intravenously on days 1 and 8 of each cycle) for a planned total of 12 cycles at 28 day intervals. The remaining 166 patients were randomised to receive no adjuvant therapy. Of the 312 patients 10 were considered unevaluable because of protocol violation (8 patients) and 2 patients because of concomitant disease (Crohns 1 patient, hypersplenism 1 patient). Details and results of this study have been reported previously [8, 9].

Locoregional or distant relapse was documented in 65/144 (45%) patients who received CMF and 111/158 (70%) of control patients by May 1991 after a median follow-up period of 9 years. A further 5 patients (2 CMF, 3 controls) had contralateral breast cancer as the only evidence of recurrent disease and have been excluded from subsequent analysis. In this report overall survival, time to relapse, survival after relapse and response to systemic therapy for the 176 patients (111 control patients and 65 CMF patients) who relapsed locally or distantly have been compared. Recurrences in the ipsilateral anterior chest wall or axillary, supraclavicular, or infraclavicular lymph nodes were defined as locoregional. Patients who had metastatic disease on restaging within 6 weeks of a locoregional recurrence were considered to have concurrent local and distant disease.

Management after relapse was determined according to standard policies of the unit. Relapse within a conserved breast was treated by mastectomy. Other locoregional recurrences (chest wall, axillary, supraclavicular or infraclavicular lymph nodes) were treated normally in the first instance by excision and/or radiotherapy. Systemic therapy was generally reserved for patients with either uncontrolled locoregional disease or widespread metastatic disease. Endocrine treatment was preferred as first-line systemic therapy unless patients had immediately life threatening disease or were known to have oestrogen receptor-negative tumours. Where possible patients suitable for endocrine treatment were entered into one of two sequential studies evaluating the efficacy of prednisolone given with ovarian ablation (premenopausal patients) or tamoxifen (postmenopausal patients) [10].

Dates of relapse and response to systemic therapy were established according to UICC criteria [11]. Survival from first histological diagnosis, time to relapse and survival after relapse for the two groups were compared using the Kaplan–Meier method [12]. Response rates to systemic therapy given after relapse for patients who had received adjuvant CMF were compared with those for controls using Fishers Exact Test. Ninety-five per cent confidence intervals for response rates were calculated [13].

RESULTS

The characteristics at the time of initial presentation for the 176 patients who relapsed are shown in Table 1. No significant imbalances in histological type or grade, oestrogen or progesterone receptor status or number of involved nodes at the time of presentation were observed between the two groups. 65/111 (59%) of the control patients were premenopausal at initial diagnosis compared with 31/65 (48%) of CMF-treated patients (Table 1). At the time of relapse (Table 2), only 14 of the CMF-treated patients were known to be premenopausal, reflecting the high incidence of drug-induced amenorrhoea.

Table 1. Characteristics of patients at first presentation, n = 176

	CMF	(%)	Control	(%)
Total	65	(45)	111	(70)
Age (years)				
Mean	49		48	
Range	25–64		23–65	
Premenopausal	31	(48)	65	(59)
Postmenopausal	34	(52)	46	(41)
Ductal				
Grade I/II	21	(32)	46	(41)
Grade III	32	(49)	40	(36)
Grade unknown	3	(5)	6	(5)
Lobular	7	(11)	12	(11)
Other	2	(3)	7	(6)
ER				
Negative	15	(23)	28	(25)
Positive	48	(74)	76	(69)
not known	2	(3)	7	(6)
PR				
Negative	28	(43)	45	(41)
Positive	35	(54)	58	(52)
not known	2	(3)	8	(7)
Node status				
1–3	25	(38)	53	(48)
> 3	40	(62)	58	(52)
Mastectomy	52	(80)	78	(70)
Conservation	13	(20)	33	(30)

ER = oestrogen receptor; PR = progesterone receptor.

The median time to relapse for CMF-treated patients was 2.2 years compared with 1.4 years for controls ($P = 0.003$, Table 2). This difference was confined to premenopausal patients, amongst whom a highly significant prolongation of time to relapse was observed for CMF-treated patients ($P < 0.0001$, Table 2). Sites of first relapse were similar between the two groups with 35% of each group relapsing locally, 46% at a distant site only and 18 and 19%, respectively, with concurrent local and distant relapse.

Survival after first relapse at any site is shown in Fig. 1. No significant difference was observed between the two groups ($P = 0.37$). 21 (95%) of the 22 CMF-treated patients who initially had locoregional recurrence only have subsequently had documented distant recurrence, compared with 26 (68%) of the 38 patients who received no adjuvant therapy (Fisher's exact test, $P = 0.02$). Survival following locoregional relapse was somewhat better for the control patients, but the difference did not achieve statistical significance ($P = 0.07$).

A total of 64 CMF-treated patients and 99 control patients have developed distant metastases. Median survival from the time of documented distant metastases was similar for the two groups (1.2 and 1.4 years, respectively, $P = 0.42$, Fig. 2). Survival from date of distant recurrence was further analysed according to menstrual status at first presentation. Median survival for premenopausal patients was not significantly different (CMF 1.3 years, control 1.2 years; $P = 0.35$, Fig. 3), whereas postmenopausal patients in the control group had a statistically significant survival advantage over the CMF group (median survival CMF 1.0 year, control 1.8 years; $P = 0.03$,

Table 2. Characteristics of patients at first relapse, n = 176

	CMF	(%)	Control	(%)	*P* value
Total	65		111		
Age (years)					
Range	26–69		24–76		
Mean	55		50		
Median time to relapse (years)					
All patients	2.2		1.4		0.003
Premenopausal at diagnosis	2.8		1.1		<0.0001
Postmenopausal at diagnosis	1.8		1.7		0.6
Menopausal status					
Pre	14	(22)	55	(35)	0.0004
Post	46	(70)	55	(50)	0.007
Uncertain	5	(8)	1	(1)	
First relapse					
Locoregional	22	(35)	38	(35)	
Local and distant	12	(18)	21	(19)	
Distant only	31	(46)	52	(46)	
Total	65		111		
Sites of first distant metastases					
Bone	21	(50)	31	(42)	
Liver	4	(10)	7	(10)	
Lung	4	(10)	10	(14)	
Soft tissue	5	(10)	8	(11)	
Pleura	1	(1)	0	(0)	
Brain	0	(0)	1	(1)	
Multiple	8	(19)	16	(22)	
Total	43	(100)	73	(100)	
Distant relapse at any time	64	(98)	99	(89)	

Fig. 4). Multivariate analysis of survival [14] after relapse amongst postmenopausal patients demonstrated that the adverse effect of prior exposure to CMF was independent of tumour size, tumour grade, number of axillary nodes involved, oestrogen and progestogen receptor levels and age.

Endocrine treatment was given to 123 of the 176 (70%) patients at some time after first relapse (Tables 3–5). The overall response rate [complete response (CR) + partial response (PR)] to primary endocrine therapy for patients who had received adjuvant CMF was 18% [95% confidence interval (C.I.) 9–33%] compared with 38% (95% C.I. 27–51%) for those who had been controls ($P < 0.05$). 110 of the 123 patients had received endocrine therapy as first salvage treatment. Overall response rate (CR + PR) for patients in the CMF group was 22% (95% C.I. 12–38%) compared with 40% (95% C.I. 28–53%) in the control group ($P = 0.07$). Time to progression following primary endocrine therapy (Fig. 5) was significantly longer for those who had received no adjuvant therapy (median 23 weeks) than for those previously treated with CMF (median 19 weeks; $P = 0.03$). When analysed according to menstrual status at presentation this benefit was confined to the postmenopausal control group ($P = 0.03$).

A total of 94 of the 176 (53%) patients received chemotherapy following relapse (Tables 6–8). In 45 cases this was the first systemic treatment for relapse and in 49 this was given after a trial of endocrine therapy. The response rate to first-line chemotherapy for relapse for those who had not received adju-

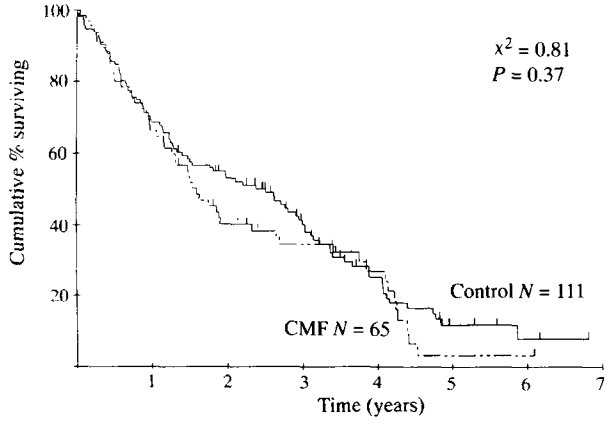

Fig. 1. Survival from first relapse.

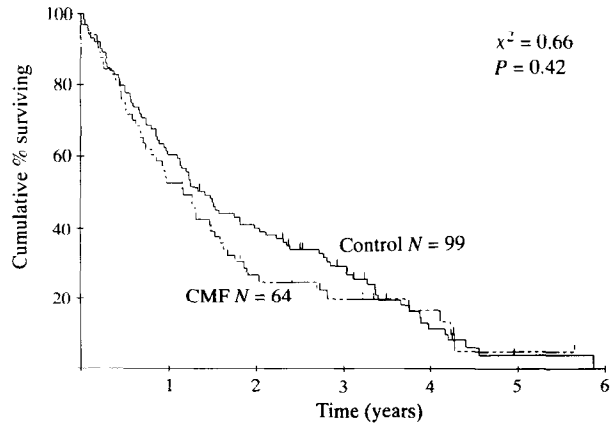

Fig. 2. Survival from first distant metastasis.

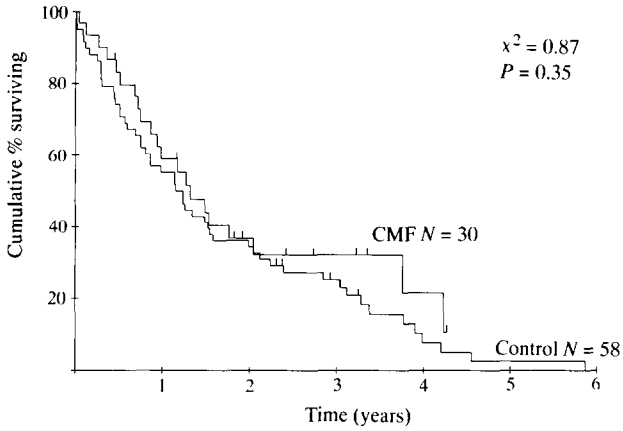

Fig. 3. Survival from first distant metastasis: premenopausal.

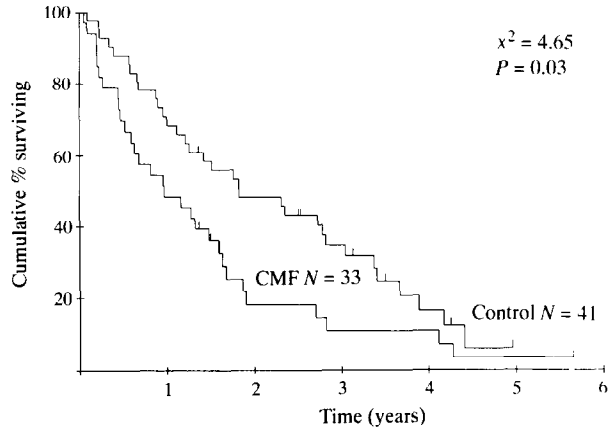

Fig. 4. Survival from first distant metastasis: postmenopausal.

Table 3. First endocrine treatment after relapse

	No. of patients CMF	Control
Tamoxifen	16	25
Tamoxifen and prednisolone	28	28
Ovarian ablation	1	8
Ovarian ablation and prednisolone	4	11
Other	0	2
Total	49	74

Table 4. Response to first endocrine treatment after relapse

	No. of patients CMF	Control	*P* value
Complete response	0	5	
Partial response	7	18	
No change	10	15	
Progressive disease	21	23	
N.A.	11	13	
Total	49	74	
CR + PR	18%	38%	< 0.05
95% C.I.	9–33	27–51	

N.A. = not assessable.

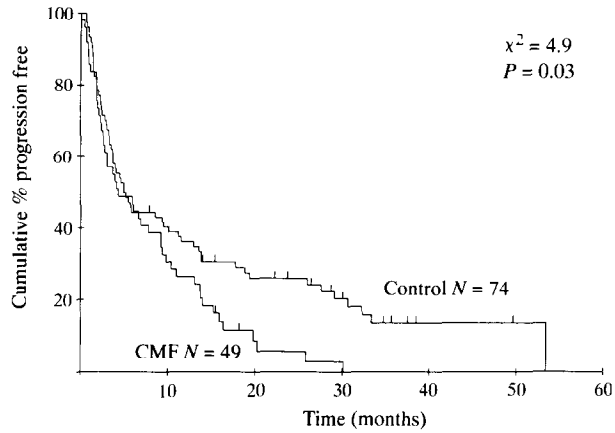

Fig. 5. Time to progression following endocrine therapy.

Table 5. Response to first endocrine treatment according to menstrual status at diagnosis

	No. of patients CMR	Control	*P* value
Premenopausal	2/15 (13%)	9/32 (28%)	0.3
Postmenopausal	5/23 (22%)	14/29 (48%)	0.08
All patients	7/38 (18%)	23/61 (38%)	< 0.05

Table 6. First chemotherapy treatment after relapse

	No. of patients CMF	Control
Doxorubicin (+/− vincristine)	12	22
CMF	3	25
Epirubicin	10	9
Mitomycin C vinblastine	6	1
Mitoxantrone	3	2
Prednimustine	0	1
Total	34	60

vant CMF was 23% (95% C.I. 11–41%) compared with 47% (95% C.I. 34–60%) for those who had been controls ($P = 0.05$). Of the 45 patients who had received chemotherapy as first-line systemic salvage treatment the response rates were again different with 48% of control patients achieving a response (95%

Table 7. Response to first chemotherapy after relapse

	No. of patients CMF	Control	*P* value
Complete response	0	1	
Partial response	6	23	
No change	8	17	
Progressive disease	12	10	
N.A.	8	9	
Total	34	60	
CR + PR	23%	47%	0.05
95% C.I.	11–41	34–60	

N.A. = not assessable.

Table 8. Response to first chemotherapy according to menstrual status at diagnosis

	No. of patients		
	CMF	Control	*P* value
Premenopausal	4/14 (29%)	17/31 (55%)	0.12
Postmenopausal	2/12 (17%)	7/20 (35%)	0.42
All	6/26 (23%)	24/51 (47%)	0.05

C.I. 30–67%) while only 10% (95% C.I. 2–40%) of those who had received prior CMF had a response ($P = 0.05$). Time to progression was longer for controls (median 17 weeks) than for patients who had received CMF (median 9 weeks, $P = 0.03$, Fig. 6). Analyses based on menopausal status again suggested most of the benefit was in postmenopausal patients although this did not achieve statistical significance ($P = 0.09$). No difference in time to progression following chemotherapy was observed between premenopausal CMF-treated patients and controls ($P = 0.3$).

DISCUSSION

The use of adjuvant chemotherapy has significantly increased the relapse-free survival and survival of premenopausal women with axillary node-positive breast cancer. Despite this, a significant number of patients will relapse and require further systemic therapy. Therefore, the question of whether prior adjuvant chemotherapy adversely affects response to subsequent systemic treatment or survival following relapse is of considerable importance.

In this study, significantly lower response rates both to endocrine therapy and chemotherapy were observed in patients who had received adjuvant CMF than in the control group. Similar low response rates have been found in other series following adjuvant chemotherapy. Buckner *et al.* (1987) evaluated salvage systemic therapy in 257 patients relapsing after adjuvant chemotherapy. Objective response rate for subsequent hormonal therapy was 29% and to subsequent chemotherapy was 28% which is considerably lower than the response rates one would expect for first-line therapy for metastatic breast cancer. Conversely, Valagussa *et al.* [7] found no significant difference in response rates between control and CMF groups for both endocrine and chemotherapy treatments. The low response rates in the current study suggest that adjuvant chemotherapy has rendered the patients less responsive to subsequent chemotherapy, indicating the possible emergence of drug resistant clones of cells.

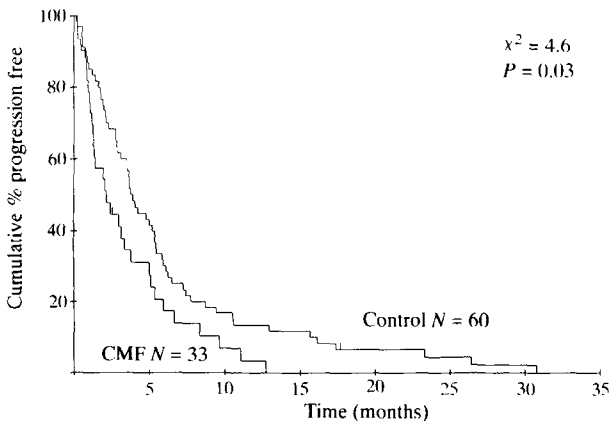

Fig. 6. Time to progression following chemotherapy.

The lower response rate to endocrine therapy given at relapse seen in patients who had received CMF is less easy to explain. It may be that patients are rendered less sensitive to hormonal treatment or alternatively may support the contention that the beneficial effect of CMF may in part be due to an endocrine mechanism [15]. Patients who are premenopausal at diagnosis and who develop amenorrhoea during adjuvant chemotherapy might be considered to have had a hormonal treatment prior to relapse. However, the difference observed in response rates and time to progression between controls and CMF-treated patients was not confined to premenopausal patients, but was in fact more marked in patients who had been postmenopausal at diagnosis. A possible explanation is that prior adjuvant chemotherapy may lower oestrogen receptor expression which in turn protects cells from the antiproliferative effect of tamoxifen. This abolition of ER expression has been reported in MCF-7 cells exposed to chemotherapeutic agents [16, 17] but was not seen in a nude mice model [18] nor in patients with breast cancer who underwent multiple biopsies for determination of oestrogen receptor status following chemotherapy [19].

In spite of significant differences in response and time to progression following systemic therapy, no survival differences were observed between the groups from date of relapse. Subgroup analysis showed, however, that postmenopausal patients who had received adjuvant CMF had significantly shorter survival after relapse than controls and that this difference was independent of other variables between the two groups ($P = 0.02$). When considering the possible difference in effect on survival between pre- and postmenopausal patients it might be argued that since many factors were examined the chances of one being significant were high. However, the effect of adjuvant CMF was only examined in relation to menstrual cycle because of known differences in effect of CMF with regard to menstrual status. We did not test for survival differences within other factors such as nodal status, tumour size, etc.

Even so, the apparent difference of effect in the menopausal subgroups should be interpreted with caution and needs further correlation from other studies. No clear explanation for this potential effect presents itself but possible adverse immunosuppressive actions of CMF could be relevant. Reports of survival following failed adjuvant chemotherapy are contradictory and no clear consensus exists. For example, Valagussa *et al.* [7] found no survival advantage for either control or CMF groups, irrespective of salvage treatment, while Ahmann *et al.* [13] found a shorter survival for patients who had received prior adjuvant chemotherapy (median survival 18 months) than for patients who had not received adjuvant therapy (median 28 months).

In conclusion, prior adjuvant chemotherapy adversely affects response rates to systemic treatment and appears to have an adverse effect on survival after relapse for postmenopausal women. The low response rates observed in this study support the inclusion of prior adjuvant chemotherapy as a stratification factor in clinical trials of chemotherapy and endocrine treatment of advanced breast cancer.

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Immunological Reconstitution After High-dose Chemotherapy and Autologous Blood Stem Cell Transplantation for Advanced Ovarian Cancer

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We evaluated the immunological reconstitution of patients who underwent high-dose chemotherapy and autologous blood stem cell transplantation (ABSCT) for advanced ovarian cancer. Sixty days after transplantation a complete reconstitution of lymphocytes and of the CD3, CD4, CD8, CD19, and CD16/56 subsets was observed in this series. A significant increase in the count of interleukin-2 receptor expressing lymphocyte (CD25) was found on day +60 after transplantation compared to that obtained at diagnosis and before transplantation. A significantly higher lymphokine-activated killer (LAK) precursor activity was seen on day +60 compared to the values obtained at diagnosis and before transplantation while natural killer activity did not show any significant variation. We conclude that ABSCT gives prompt and complete immunohaematopoietic reconstitution after high-dose treatment. Moreover, our data support the feasibility of interleukin-2/LAK therapy as consolidative therapy after ABSCT.
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INTRODUCTION

HIGH DOSE chemotherapy and autologous bone marrow transplantation (ABMT) have now become an important treatment modality for patients with haematological and solid tumours [1–5].

More recently, the utilisation of autologous blood stem cell transplantation (ABSCT) [6–8] has significantly shortened the drug-induced myelosuppression compared to ABMT [9, 10]. Several reports described the kinetics of the immunological recovery after intense chemotherapy without stem cell rescue [11] or high dose chemotherapy followed by ABMT [12–15]. On the other hand, only preliminary data are available for patients receiving ABSCT after high dose chemotherapy [16]. Generally, following ABMT, a delayed lymphocyte recovery mainly due to a decrease in the $CD4^+$ subset is observed; in contrast an increase is observed in $CD8^+$ and in activated T and natural killer (NK) subsets [12–15]. Furthermore, Higuchi *et al.* [17] have recently indicated that lymphokine-activated killer (LAK) precursor