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Original Paper

Very Low-dose Adjuvant Chemotherapy in Steroid Receptor Negative Stage I Breast Cancer Patients

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A randomised clinical trial was performed to test whether or not low-dose chemotherapy lasting only 35 days improves the outcome of breast cancer patients with stage I disease and negative oestrogen and progesterone receptors (ER-, PgR-). Between 1984 and 1990, 277 stage I breast cancer patients with tumours negative for both oestrogen and progesterone receptors were randomised to receive either low-dose short-term chemotherapy or no chemotherapy. Chemotherapy consisted of one cycle of doxorubicin, vincristin (AV) and one cycle of cyclophosphamide, methotrexate, fluorouracil (CMF). Patients were stratified for tumour stage, type of surgery, menopausal status and participating centre. Results were analysed both by univariate and multivariate statistical. After a median length of follow-up of 84 months, disease-free (DFS) and overall survival (OS) did not differ significantly between patients having received adjuvant chemotherapy and the control group. Uni- and multivariate analysis did not show any significant prognostic or therapy related factor. A low-dose short-term adjuvant chemotherapy is insufficient to improve the prognosis of patients with breast cancer stage I with ER-, PgR-tumours. © 1998 Published by Elsevier Science Ltd.

Key words: breast cancer, chemotherapy, adjuvant

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INTRODUCTION

ADJUVANT CHEMOTHERAPY has been shown to improve prognosis in patients with node-negative disease, especially with oestrogen receptor (ER)-negative tumours [1–8]. These beneficial results have been gained either by a short-term peri-operative chemotherapy course [3, 6] or by long-term poly-chemotherapy administration [1, 2, 4, 5, 7, 8]. In general, the therapeutic effect of adjuvant chemotherapy is clearly age dependent, but independent of nodal status [9].

Usually chemotherapy protocols last 6–18 months and are often associated with serious medical and psychological side-effects, often severely affecting patients' quality of life [10], and sometimes resulting in treatment delay or cessation [11]. For patients with low risk of relapse, in particular, the benefits of therapy have to be weighed against the potential adverse effects of treatment. Patients have to choose between

these adverse effects versus an undefined risk reduction for relapse and/or death from the disease. Often patients are unable to do this properly and doctors are confused in counselling them because these risks cannot be precisely described, in particular not for an individual patient. Hence, data are urgently needed for the effectiveness of different types of cytotoxic chemotherapy in patient subgroups at different stages of risk of relapse or death from the disease.

Clearly the length and the dose of adjuvant chemotherapy are the most important factors sometimes causing substantial morbidity [12]. Recently, there have been several attempts to minimise side-effects by reducing dose and duration of cytotoxic treatment or even both in order to reduce treatment-related side-effects [13].

Currently there is no information gained from prospective randomised trials about the necessary duration and dose intensity of adjuvant chemotherapy in stage I disease. For stage II breast cancer, there exist both retrospective analyses [14] and prospective trials [13] indicating that patients receiving either full-dose CMF or FEC show a longer disease-free and overall survival.

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Among patients with stage I disease, the patient subgroup with steroid hormone receptor negative breast cancers forms an interesting subgroup. Receptor negativity has been demonstrated to be associated with a higher incidence of high histological grade [15] and may reflect a more aggressive biological behaviour of the tumour [16]. In general, node-negative patients with steroid hormone receptor negative tumours represent a subgroup with a highly aggressive tumour, treated at an early stage of the disease. Their outcome may depend on tumour size, ranging from 64 to 80% disease-free survival at 5 years [17].

In order to address the question of dose intensity in this patient group with relatively low-risk breast cancer, the Austrian Breast Cancer Study Group initiated a trial in 1984 to determine whether a low-dose short-term chemotherapy can improve the outcome of patients with stage I, ER-, PgR- (progesterone receptor) breast cancer compared with an untreated observational control. The type of chemotherapy used lasted only 35 days and included three administrations of cytotoxics on an outpatient basis. We report mature data with a median follow-up of 6.5 years with 23% of patients having experienced relapse.

PATIENTS AND METHODS

Women under 70 years of age with histologically confirmed primary unilateral breast cancer (pT1b to pT3a) were eligible for this nationwide multicentre trial when they had no axillary lymph node metastases, assessed by histopathological examination and had ER- PgR- primary tumours. Patients with tumours smaller than 5 mm in diameter were excluded in the node-negative setting, as were women with bilateral breast cancer, evidence of distant metastases, documented history of other cancer except cured basal cell carcinoma of the skin or early cervical cancer, pregnancy or lactation or serious medical or emotional problems.

Between 1984 and 1991, 290 patients were entered from 21 participating centres in Austria. 277 patients fulfilled the entry criteria and form the basis for this evaluation. 13 patients were excluded from all analyses because they were found not to fulfill all inclusion criteria. Stratification criteria included menopausal status, tumour size, operative procedure and participating centre and were included in the randomisation process using the method of Pocock and Simon [18]. After informed consent, patients with ER- PgR- tumours and negative axillary nodes were randomised to an untreated control group or to postoperative chemotherapy consisting of doxorubicin 20 mg/m² and vincristine 1 mg/m² on day one and cyclophosphamide 300 mg/m² methotrexate 25 mg/m² and 5-fluorouracil 600 mg/m² on days 29 and 36 (AV-CMF), administered intravenously. Cytotoxic treatment started no longer than 4 weeks after surgery.

Surgical treatment consisted either of modified radical mastectomy or breast preservation with negative margins plus axillary clearance. Axillary clearance always included complete levels I and II and dissection of level III was optional [19]. At least 8 axillary lymph nodes had to be investigated by histological examination.

The local pathologist was responsible for the histological preparation of the surgical specimen. The tissues were fixed in formalin, embedded in paraffin, sectioned and stained in haematoxylin-eosin. Tumour size was determined from the fixed specimen. Histological grade was judged according to Bloom and Richardson [20]. ER and PgR content were

measured by dextran-coated charcoal titration with Scatchard analysis of tumour samples frozen directly in the operation theatre [21]. Values greater than 10 fmol/mg cytosol protein were considered positive. Quality controls were performed by regular exchange of samples among labs. Thus, only patients with tumours with both ER and PgR lower than 10 fmol/mg protein were eligible for analysis.

The indication for postoperative irradiation was left to the discretion of the local surgeon. In general, patients with breast conservation received a standard dose of 50 Gy to the remaining breast tissue without irradiation of the axilla. After modified radical mastectomy, patients were not usually irradiated. In patients receiving AV-CMF, radiotherapy started after completion of chemotherapy. In the control group, patients were irradiated after wound healing.

All patients were regularly followed at least every 3 months for the first 3 years and with 6 month intervals thereafter, as described previously [22]. Routine evaluation of the patients included clinical examination and laboratory analyses including tumour markers, CEA and CA15-3. Chest X-rays, liver ultrasound and mammography were performed every year, or more frequently if clinically indicated. Patients' first relapse and death served as study endpoints. A suspicious tumour within the operation field was biopsied to confirm local relapse.

All patient data were collected at a central data documentation centre of the study group. Data were stored and processed in an IBM 3090 mainframe computer of the University of Vienna using SAS software. Sample size calculation was done by the method of George and Desu [23] based on the following assumptions: reduction of recurrences by one third (70 versus 80% DFS) at 5 years, accrual and follow-up period 5 years, alpha < 0.05, power 0.8: 283 patients in this trial would have been sufficient to detect this difference.

The value of the prognostic factors (covariates) was determined according to statistical models, with the use of BMDP. Overall survival (OS) was expressed as the number of months from the date of primary treatment of breast cancer until death. Disease-free survival (DFS) was defined as the interval between the day of surgery and the first recurrence of breast cancer. Patients who died due to reasons other than breast cancer, without any signs of breast cancer recurrence, were considered censored for all analyses. Curves for all analysis were calculated according to the method of Kaplan and Meier [24]. Differences between curves were assessed by Mantel's log-rank for censored data on survival [25].

Multivariate analysis included six covariates all of which—after appropriate testing—were considered as fixed (not time-dependent). For optimal categorisation of continuous covariates, univariate comparison was performed with chi square values. The prognostic value of the different covariates was evaluated with the use of the product-limit estimate of survival function. Covariates were entered into a Cox-proportional hazards model [26]. Covariates were selected in a stepwise manner (backward to forward) with use of a maximum likelihood ratio. A *P* value of 0.15 was adopted as the limit for the inclusion of a covariate.

Data in this study were obtained from 277 eligible patients. 13 (4.5%) patients were randomised, but turned out to be ineligible for various reasons (Table 1). The median observation time was 86 months. For this analysis, no patient was lost to follow-up, and all analyses were based on the intention-to-treat basis.

Table 1. Trial information

Randomised	290
Eligible	277 (95.5%)
Not eligible	13 (4.5%)
exclusion criterion detected during audit	6
randomisation data corrected	3
follow-up failure	2
patients choice	2
Median observation time	86 months

Table 2. Characteristics of 277 patients at the time of enrolment in the study. All values are absolute numbers

Characteristics	Chemotherapy 136	Control 141
Menopausal status		
premenopausal (<i>n</i> = 134)	67	67
postmenopausal (<i>n</i> = 143)	69	74
Tumour size (cm)		
<2 (<i>n</i> = 140)	73	67
2–5 (<i>n</i> = 124)	55	69
>5 (<i>n</i> = 13)	8	5
Tumour grading		
G1, 2, x (<i>n</i> = 174)	85	89
G3 (<i>n</i> = 103)	51	52
Tumour histology		
lobular (<i>n</i> = 23)	17	6
ductal (<i>n</i> = 254)	119	135
Type of surgery		
mastectomy (<i>n</i> = 185)	90	95
breast conservation (<i>n</i> = 92)	46	46
Radiotherapy		
yes (<i>n</i> = 90)	42	48
no (<i>n</i> = 187)	94	93

Characteristics of eligible patients are shown in Table 2. Stratification factors were well distributed between the two groups. Other factors not used for the stratification were also well balanced.

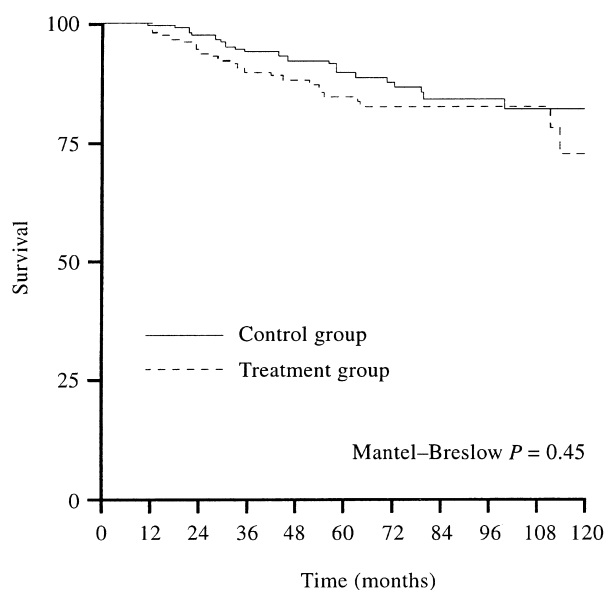
RESULTS

Disease-free survival, overall survival

At a median follow-up of 7 years, relapses occurred in 63 patients (22.7%). 43 patients died from breast cancer (15.5%). In the treatment group, 31 patients relapsed and 23 died; in the control group 32 patients relapsed and 20 died.

Table 3. Prognostic factors—univariate comparison

	Overall survival at 7 years (%)		DFS at 7 years (%)	
		<i>P</i>		<i>P</i>
Treatment				
Control	86.5	0.45	77.2	0.87
AVCMF	84.6		77.4	
Menopause				
Pre	85.8	0.92	80.6	0.60
Post	85.3		76.9	
Tumour size				
≤ 2 cm	87.1	0.54	78.6	0.80
> 2 cm	84.2		78.4	
Grading				
G1–2	90.4	0.19	76.0	0.73
G3	82.5		78.1	

Figure 1. Overall survival (*n* = 277 patients).

DFS curves for all eligible patients showed no statistical difference between treatment and control group (*P* = 0.87). The relapse-free rate at 7 years was 77% for both groups. When OS curves for patients receiving short-term chemotherapy were compared with patients with no chemotherapy, again no statistical significant difference was found, *P* = 0.45 (Figure 1). At the median follow-up time of 84 months, the estimated overall survival was 86% in the control group and 83% in the treatment group.

Prognostic factors

In Table 3, the 7 years OS and DFS are shown according to univariate analysis of prognostic factors. No significant differences were observed. With multivariate analysis, six covariates were included for determination of independent prognostic power: tumour size, grading, histological type, age, adjuvant therapy and surgical procedure. No factor included in the multivariate model had a significant prognostic impact. Interaction of several prognostic factors including age and grading with allocated treatment were tested and found to be non-significant.

Site of recurrence

The distribution of sites of recurrences is shown in Table 4. Again, no significant differences between the treatment group and the control group were found.

Toxicity

Except for alopecia (WHO grade II: 18%, WHO grade III: 2%) no therapy-related side-effects > WHO grade I were

Table 4. Site of recurrence (cumulative)

	Chemotherapy	Control
Local (chest wall, skin)	7	14
Lung/pleura	1	2
Bone	9	7
Liver	3	3
Local and distant sites	5	3
Multiple distant sites	9	5

recorded for the patients in the treatment group. All treated patients completed the adjuvant chemotherapy and no dose reductions or time delays were necessary.

DISCUSSION

The results of this randomised multicentre trial clearly demonstrate that a low-dose short-term chemotherapy—although including doxorubicin—is insufficient to improve the prognosis of patients with hormone-independent node-negative breast cancer.

At the time of the initiation of this trial, the role of chemotherapy in this patient group, with a relatively low risk of recurrence, was unclear. Results of our own group and others [4, 6, 8] showed some marginal beneficial effect of adjuvant treatment, but it was not before 1989 that several reports from large trials [1, 5, 7] indicated a significant benefit of postoperative adjuvant chemotherapy in this patient group. However, with the few data available from large cohorts with extended follow-up, node-negative breast cancer seems to be a curable disease by surgery alone [17]. With a 20-year DFS of 80 per cent, irrespective of the receptor status, the addition of any adjuvant cytotoxic treatment may not be worthwhile, particularly with a suboptimal dose intensity.

What we attempted with our trial was to identify a subgroup of stage I disease patients who would benefit from adjuvant cytotoxic treatment. By reducing dose intensity apparently too radically, the treatment failed to improve patients' survival.

Other attempts to identify a subgroup of node-negative breast cancer patients with increased risk have included newly derived factors, such as p185neu oncoprotein, which seems to be associated with worse prognosis [27]. Probably other factors have to be included in the decision to suggest adjuvant cytotoxic treatment for patients with node-negative receptor-negative breast cancer. Recently, the presence or absence of tumour cells in the bone marrow at the time of surgery has been reported to be associated with a higher risk of relapse; cathepsin D seems to be a predictive factor in tamoxifen-treated hormone receptor positive disease, but the series of these data are often small and follow-up is often insufficiently low. Furthermore, technical problems and cost of these investigations are substantial [28, 29].

An individualised treatment regimen is often required in order to determine an optimal cost-benefit ratio for a given patient. This was the reason why we tried to investigate the effect of a relatively low dose intensity regimen. The results are discouraging, especially in the context of the observation that patients' individual risk factors are often not included in the decision-making process about adjuvant treatment in routine medical practice [30].

Do patients with stage I disease need chemotherapy at the same dose and duration as those with positive nodes? Results from stage II disease indicate that the duration of chemotherapy can be shortened, to some extent, without any apparent decrease in effect [31–34], but there seems to be a critical length, indicating that an extremely short duration of chemotherapy may be suboptimal, administered either directly after surgery [35] or with a delay of several weeks [36]. Wood and co-workers [13] report that reduction of dose intensity below a critical level is significantly less effective in preventing recurrence compared with moderate or high intensity. However, further dose intensification failed to achieve an additional benefit [37]. Data from the NSABP

B13 showed that cytotoxic treatment in an appropriate dose intensity results in a 27% relative reduction of treatment failure even in hormone receptor negative patients, with the conclusion that no subgroup of node-negative patients have such a good outcome as to preclude the use of effective systemic therapy in their treatment [38]. The International Breast Cancer study group (former Ludwig group) conducted a trial (trial V) in 1275 subjects with stage I disease, where peri-operative cytotoxic treatment was almost ineffective in hormone-positive cancers, but achieved a significant DFS advantage at 5 years of follow-up in oestrogen receptor negative tumours [39]. Additionally, the overview data of the EBCTCG show beyond any doubt that chemotherapy works to the same extent in patients with stage I disease as in those with positive nodes, although the absolute effect of therapy is significantly greater in patients at higher risk. However, the absolute benefit in OS is not more than 4% in favour of chemotherapy-treated patients [9]. It is interesting that, although convincing data are limited on the effectiveness of adjuvant cytotoxic treatment in the subgroup of node-negative, receptor-negative patients, most specialists believe in the effectiveness of the treatment [40].

Taking these results together, there seems to be an optimal schedule which should not be altered, either the duration or the dose. In this context, great emphasis should be placed in the future towards the identification of factors which predict response to or benefit from adjuvant chemotherapy. Preliminary results of a small trial of our group have indicated that patients with ER- tumours may obtain more benefit from adjuvant chemotherapy [41]. Recent trials on the response to adjuvant chemotherapy and overexpression of erbB-2 or S-phase suggest that it could be possible to identify factors that could relate to response to adjuvant chemotherapy [42–44]. However, all these results again relate to patients with stage II disease.

Future trials are needed in stage I breast cancer to clarify the lower limit of dose and duration of chemotherapy. Until these results are available, physicians should be cautious in suggesting a moderately dosed adjuvant cytotoxic treatment regimen to patients with hormone receptor-negative node-negative breast cancers. Patients should be informed that most probably there is some beneficial effect of full-dose chemotherapy for their postoperative prognosis. However, the absolute benefit of this approach might be rather small. Whether or not to accept the morbidity and side-effects of chemotherapy for this relatively small benefit, should be judged carefully and patients must be able to base their decision on solid information and counselling by their doctors.

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APPENDIX: AUSTRIAN BREAST CANCER STUDY GROUP

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