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Randomised Trial: One Cycle of Anthracycline-Containing Adjuvant Chemotherapy Compared with Six Cycles of CMF Treatment in Node-Positive, Hormone Receptor-Negative Breast Cancer Patients

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Key Words
Breast cancer · Chemotherapy · Adjuvant therapy

Summary
Aim: A randomised, controlled clinical trial was initiated in 1984 to test whether 1 cycle of anthracycline-containing adjuvant chemotherapy improves the outcome of breast cancer patients presenting with stage II disease and negative oestrogen and progesterone receptors (ER, PgR), as compared with 6 cycles of dose-reduced CMF. **Patients and Methods:** Within 7 years 263 women with stage II breast cancer were randomised either to receive 1 cycle of doxorubicin, vinblastine, cyclophosphamide, methotrexate and 5-fluorouracil (AV-CMF) or to receive 6 cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF). Patients were stratified for tumour stage, nodal stage, menopausal status, type of surgery and participating centre. **Results:** After a median follow-up of 100 months, neither disease-free (DFS) nor overall survival (OS) differed significantly between the two groups. **Conclusions:** Compared to 6 cycles of a non-standard low-dose CMF regimen 1 cycle of anthracycline-containing adjuvant chemotherapy failed to improve the outcome in women with stage II receptor-negative breast cancer in terms of DFS and OS.

Schlüsselwörter
Brustkrebs · Chemotherapie · Adjuvante Therapie

Zusammenfassung
Ziel: 1984 wurde eine randomisierte, kontrollierte klinische Studie initiiert, um zu testen, ob ein Zyklus einer Anthrazyklin-haltigen adjuvanten Chemotherapie das Gesamtüberleben bei Brustkrebspatienten mit einer Erkrankung im Stadium II mit negativen Östrogen- und Progesteronrezeptoren (ER, PgR) im Vergleich mit 6 Zyklen eines dosisreduzierten CMF-Schemas verbessert. **Patienten und Methoden:** Über einen Zeitraum von 7 Jahren wurden 263 Frauen mit Brustkrebs im Stadium II randomisiert, um entweder einen Zyklus mit Doxorubicin, Vinblastin, Cyclophosphamid, Methotrexat und 5-Fluorouracil (AV-CMF) zu erhalten oder 6 Zyklen mit Cyclophosphamid, Methotrexat und 5-Fluorouracil (CMF). Die Patienten wurden stratifiziert nach Tumorstadium, Lymphknotenstatus, Menopausenstatus, Art der Operation und nach teilnehmendem Zentrum. **Ergebnisse:** Nach einer medianen Beobachtungszeit von 100 Monaten unterschieden sich die beiden Gruppen weder hinsichtlich krankheitsfreiem Überleben (DFS) noch hinsichtlich Gesamtüberleben (OS) signifikant. **Schlussfolgerung:** Bei Patientinnen mit Rezeptor-negativem Brustkrebs im Stadium II konnte im Vergleich zu 6 Zyklen eines «low-dose» CMF Schemas durch die Gabe von einem Zyklus Anthrazyklin-haltiger adjuvanter Chemotherapie weder eine Verbesserung des DFS noch des OS erreicht werden.

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Introduction

The use of adjuvant chemotherapy in breast cancer patients has clearly shown to improve outcome in terms of disease-free (DFS) and overall survival (OS) [1–7]. Two groups of breast cancer patients have particularly been believed to benefit from chemotherapy and thus been treated: patients with node-positive disease irrespective of hormone receptor status and those with node-negative disease and hormone receptor-negative tumours.

In general it has been shown that DFS and OS is poorer in women with node-positive breast cancer, when treated with surgery alone with a median DFS of 30% and OS of 40% at 10 years [6]. In node-negative patients with hormone receptor-negative tumours, at 10 years DFS is 54% and OS is 63% with surgery alone.

When the trial presented in this paper was launched in 1984, numerous prospective randomised trials investigating different chemotherapeutical substances, dosages and durations of treatment were under evaluation, alongside trials addressing the issue of optimal timing of various therapeutic regimens. Most approaches tested since then have been designed in terms of a randomised comparison between an investigational schedule and conventional CMF (cyclophosphamide, methotrexate and 5-fluorouracil) treatment, the adjuvant cytotoxic treatment of choice in the early 1980s.

Prior to taxane availability, doxorubicin showed to be the most effective drug in metastatic breast cancer, producing remarkable responses even when used as single agent [8]. However, it has notable cumulative cardiotoxicity [9, 10]. No definite results were available in 1984 to estimate the value of using doxorubicin in addition to multidrug combinations in the adjuvant setting.

Against this background, the Austrian Breast and Colorectal Cancer Study Group (ABCSG) initiated a trial in 1984 in order to address the following questions:

– Does 1 cycle of adjuvant chemotherapy containing doxorubicin – the most active drug in breast cancer at that time – improve the outcome of women with steroid-receptor negative stage II breast cancer in comparison with 6 cycles of CMF?
– Is the toxicity profile of such an approach favourable compared with CMF, leading to better treatment compliance of the patients?

We report mature data with a median follow-up of 8.3 years and 56% of patients having experienced relapse.

Patients and Methods

In 1984 a randomised trial was initiated by the Austrian Breast and Colorectal Cancer Study Group in receptor-negative patients with positive axillary nodes. The study was performed as a multicentre trial, accruing patients in 21 different cancer centres across this country. Within 7 years a total of 263 patients were entered of whom 245 were eligible and included in the final analysis. 18 (6.8%) patients were excluded from all analyses because they did not fulfil all inclusion criteria for various reasons (table 1). Women younger than 70 and above 18 years of age with histologically confirmed primary unilateral breast cancer (pT1b to pT3a) with involved axillary nodes were eligible when their primary tumours were negative for both ER and PgR. Patients with tumours smaller than 5 mm in diameter were excluded, together with those showing bilateral breast disease, 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 conditions or problems. No previous irradiation or preoperative antineoplastic treatment was allowed.

Table 1. Trial information

Randomised patients, n	263
Eligible, n	245 (93.2%)
Ineligible, n	18 (6.8%)
Exclusion criterion detected during audit	
Receptor positivity, n	8
Age >70 years, n	7
Other, n	3
Median observation time, months	100

Table 2. Patient characteristics

	Treatment group	
	CMF, n	AV-CMF, n
Patients	124	121
Menopausal status		
Premenopausal	55	58
Postmenopausal	69	63
Age, years		
<50	49	57
>50	75	64
Tumour size, cm		
<2	44	42
2–5	71	67
>5	9	12
Nodal status, number of involved nodes		
1–3	66	65
4–10	48	44
>10	10	12
Tumour grading		
G1.2,x	68	61
G3	53	59
Tumour histology		
Lobular	7	12
Ductal	117	109
Type of surgery		
Breast conservation	27	33
Modified radical mastectomy	97	88
Irradiation		
Yes (n = 70)	32	38
No (n = 175)	92	83

CMF: cyclophosphamide, methotrexate, fluorouracil; AV-CMF: doxorubicin, vinblastine, cyclophosphamide, methotrexate, fluorouracil.

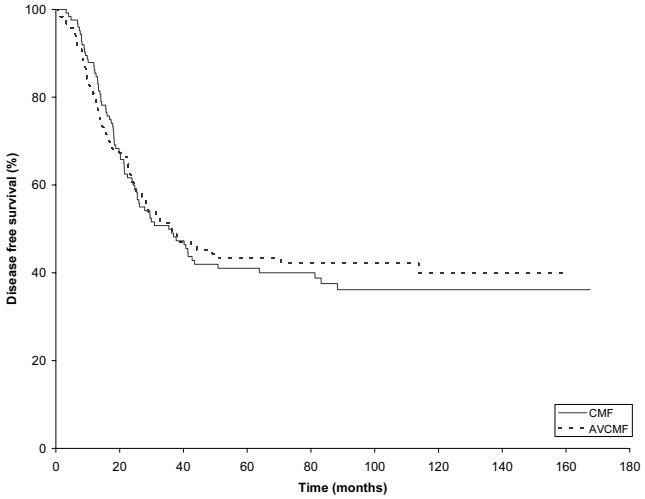

Fig. 1. Disease-free survival (n = 245 patients, p = 0.95).

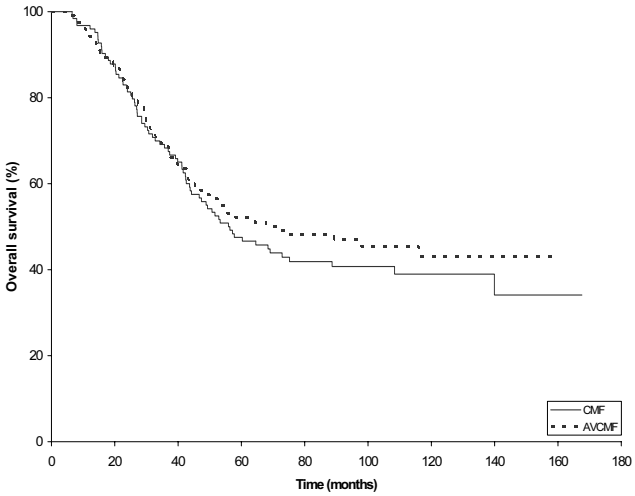

Fig. 2. Overall survival (n = 245 patients, p = 0.45).

Surgical treatment consisted either of modified radical mastectomy or breast-conserving procedure, both including axillary clearance. At least 8 axillary lymph nodes had to be removed and investigated histologically. Tumour size was determined from fixed specimens; histological grade was judged according to Bloom and Richardson [11]. Only patients for whom both ER and PgR levels did not exceed 10 fmol/mg cytosol protein were entered in the study and eligible for analysis.

Stratification criteria included menopausal status, tumour size, number of involved lymph nodes (1–3, 4–9, 10+), grading, operative procedure and participating centre, and were used in an adaptive randomisation process according to Pocock and Simon [12].

Upon giving informed consent and receiving surgery, patients were randomly assigned to receive either treatment A: 6 cycles of CMF (cyclophosphamide 500 mg, methotrexate 25 mg and fluorouracil 1,000 mg given intravenously on days 1 and 8 and repeated on day 29, administered for a total of 6 cycles), or treatment B: 1 cycle of AV-CMF (doxorubicin 50 mg/m^2 and vinblastine 5 mg given intravenously on day 1, and cyclophosphamide 500 mg, methotrexate 25 mg and fluorouracil 1,000 mg administered intravenously on days 21 and 28). Cytotoxic treatment started no longer than 4 weeks after surgery.

Upon completion of chemotherapy, all patients undergoing breast conservation and some patients treated with modified mastectomy received irradiation therapy with a standard dose of 50 Gy, the axilla being excluded from irradiation (table 2).

Follow-up examinations were done in 3-month intervals within the first 3 years and in 6-month intervals thereafter. Routine evaluation included physical examination and laboratory analyses including tumour markers CEA and CA 15–3. Chest X-rays, liver ultrasound and mammography were performed annually, or more frequently if clinically indicated.

Patients met the primary study endpoints for DFS and OS in case of occurrence of first relapse or death, respectively. Whenever possible, a local or regional recurrence had to be confirmed histologically.

All patient data were collected at the Study Group central data office and stored, processed and analysed applying SAS software (SAS Institute Inc., 1996).

Sample size calculation was based on the following assumptions: reduction of recurrences by 20% (55–65% DFS) at 5 years, a 5-year accrual and follow-up period, $\alpha < 0.05$, power 0.85. Time to first relapse or death was estimated and graphically presented according to the method of Kaplan and Meier [13]. Differences between curves were assessed by Mantel's log-rank test for censored survival data [14]. Data from 245 eligible patients in this study were obtained within a median observation time of 100 months. Stratified patient characteristics of eligible participants were evenly distributed in the two treatment arms and all factors were well balanced (table 2).

Table 3. Number and sites of recurrence

Recurrence	Treatment group	
	CMF, n	AV-CMF, n
Local (chest wall, skin)	18	18
Lung/pleura	6	4
Bone	14	12
Liver	1	2
Other	11	12
Local and distant sites	6	6
Multiple distant sites	20	27

Results

Disease-Free Survival, Overall Survival

After a median duration of 8.3 years of follow-up, relapses occurred in 137 patients (55.9%), 133 patients (97.1%) of whom died from breast cancer in the meantime (<160 months observation time). In treatment arm A (6 cycles CMF), 69 patients relapsed and all of these patients died. 4 additional patients in this group died from reasons other than cancer. In treatment arm B, 68 patients relapsed, 64 of whom deceased.

All patients were available for follow-up with respect to survival status due to the use of a centralised national population registry. DFS curves for all eligible patients showed no statistical difference between the two treatment arms, p = 0.95 (fig. 1). Likewise, a comparison between the two treatment arms in terms of OS identified no statistically significant difference. After a median follow-up of 8.3 years, an estimated proportion of 41 and 47% survived in treatment arms A and B, respectively p = 0.45 (fig. 2).

Site of Recurrence

The distribution of sites of recurrences is shown in table 3. Again, no significant differences emerged between treatment arms A and B.

Toxicity

In treatment arm A, the side-effects frequently observed were nausea and vomiting WHO grade I and II (in 78% of the cycles), stomatitis grade I was seen in less than 10% of cycles, and alopecia WHO grade I occurred in 50% of patients, no relevant myelotoxicity resulting in a delay of treatment application was seen. No other therapy-related side-effects beyond WHO grade I have been reported and no toxicity-associated dose reductions were necessary.

The patients in treatment arm B did even better. The only observed treatment-related side-effects WHO grade I were nausea and stomatitis in less than 20% of patients. The treatment was very well tolerated and no reduction in dose was necessary within the course of application.

Discussion

This trial is one out of a series of 4 randomised trials conducted between 1984 and 1991 by the Austrian Breast and Colorectal Cancer Study Group, including more than 1,100 women, to evaluate the hypothesis whether it is possible to avoid significant and serious toxicity known to be relevant in the use of conventional chemotherapy with CMF by shortening the duration of therapy and including doxorubicin instead. The results of the other trials in this series have been reported elsewhere [15, 16].

To date, several trials have indicated that the duration and/or dose of adjuvant chemotherapy can be reduced to some extent without any apparent decrease in effect, but there seems to be a critical minimal duration and/or dose intensity of treatment [8, 17]. An extremely shortened duration of chemotherapy has been reported to be suboptimal, whether administered directly after surgery or with several weeks of delay [18, 19]. Bonadonna [1] reported that reduction of classical CMF dose below a critical level is significantly less effective in preventing relapse than full-dose or nearly full-dose CMF treatment, these results being in line with overview data published by Goldhirsch [20, 21].

Both as a single agent and in various combinations, doxorubicin was the first drug to show remarkable activity in metastatic disease. Thus, by the mid-eighties, it was consecutively implemented within adjuvant clinical trials. In most of these studies, doxorubicin was added to the classical CMF regimen in node-positive breast cancer patients to improve the prognosis of these patients. Superiority in results over CMF alone was gradually evidenced [22]. The NSABP B-15 trial indicated that including doxorubicin results in potentially shortened adjuvant treatment without activity losses [23].

Together with the improvement of adjuvant chemotherapy efficacy, quality of life during treatment has been stated to be a key issue [24, 25]. The attempt to reduce impairment of patients treated with adjuvant chemotherapy has been an objective in various trials. Several attempts were made to minimise side-effects by reducing the dose and duration of cytotoxic treatment, which sometimes severely affect patients' quality of life [10, 15–17, 20, 24–26]. Conflicting information has accumulated from several randomised trials using a single-cycle regimen of adjuvant chemotherapy [15, 16, 18].

In the mid-eighties, the study presented here was started with receptor-negative, node-positive patients to evaluate the hypothesis of an improved outcome using a short-term cytotoxic treatment including doxorubicin against applying a CMF regimen.

Overall, we were unable to establish DFS or OS improvements in the short-term anthracycline-containing treatment group compared with 6 cycles of a non-standard dose-reduced CMF treatment. One could argue that this might have been also the case if we had tested the treatment with radical dose reduction we used in both arms against a control arm without any chemotherapy. Our efforts to avoid treatment-related toxicity that would affect patients' quality of life resulted in (i) a potentially critical reduction of dose in CMF treatment as well as (ii) a possibly crucial shortening of duration of chemotherapy in spite of doxorubicin inclusion. Altogether, our results may be explained by a reduced dose intensity that could have been especially crucial in patients with nodal involvement. Within the past decade, dose-reducing attempts have lost their importance in avoiding treatment-related toxicity due to the development of highly effective antiemetics, antibiotics and cytokines for supportive treatment.

Appendix

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