

Impact of anthracycline dose on quality of life and rehabilitation in breast cancer treatment

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ABSTRACT

Background: In 2005 the Dutch national guidelines for treatment of breast cancer were updated. From then onwards, patients with operable breast cancer, who formerly received four cycles of adjuvant chemotherapy with doxorubicin/cyclophosphamide (AC), were treated with five cycles of 5-fluorouracil/epirubicin/cyclophosphamide (FEC), based on data suggesting survival benefit.

Primary objective: evaluation of the effect on quality-of-life and trainability after four AC versus five FEC cycles of polychemotherapy. **Secondary objective:** evaluation of the effectiveness of an 18-week training programme for breast cancer survivors.

Methods: A prospective cohort study design was used, comparing two chemotherapy regimens historically. The first cohort (group 1) received 4AC (A 60 mg/m², C 600 mg/m²) (n=25) and the second cohort (group 2) received 5FEC (F 500 mg/m², E 90 mg/m², C 500 mg/m²) (n=50) adjuvant polychemotherapy. Both groups completed an 18-week high-intensity strength-training programme. **Outcome measures** were changes in quality-of-life (EORTC-QLQ-C30, MFI-20), muscular strength (one-repetition maximum; leg press) and cardiopulmonary function (VO₂max) between baseline and follow-up.

Results: Between March 2002 and February 2006, 75 female subjects with breast cancer participated in this study. Baseline characteristics were similar in both groups. After completing the training programme, both groups showed a significant improvement in all outcome measures. No significant differences in changes of the EORTC-QLQ-C30 and MFI-20, one repetition maximum of the leg press and the VO₂max between the two groups were demonstrated.

Conclusion: After adaptation of the Dutch national breast cancer treatment guidelines, patients received prolonged and increased doses of anthracyclines. This, however, did

not result in a difference in the baseline situation before rehabilitation and in training response, nor in quality of life between the two groups.

KEYWORDS

Anthracycline treatment, operable breast cancer, quality of life

INTRODUCTION

More women survive breast cancer than any other type of cancer, partly owing to the improved treatment possibilities. Therefore, the need to learn more about the effect of adjuvant chemotherapy on (long-term) quality of life (QoL) is growing. Breast cancer patients, who are subjected to adjuvant chemotherapy, suffer from emotional and physical side effects. Fatigue and loss of physical performance are the most frequently reported symptoms by (breast) cancer patients. This is mainly caused by an impaired cardiopulmonary function and diminished muscular strength.¹ Many of these patients perceive fatigue as the most distressing symptom associated with their illness because it imposes limitations on their physical activity level.²

Other side effects are nausea, pain, changes in body composition, changes in mood state and sleep difficulties.¹

In 2005 the Dutch national guidelines for treatment of breast cancer were updated. From then onwards, patients with operable breast cancer, who formerly received four cycles of adjuvant chemotherapy with doxorubicin/

cyclophosphamide (AC), were treated with five cycles of 5-fluorouracil/epirubicin/cyclophosphamide (FEC), based on data suggesting survival benefit.³ However, no data are available on the extent to which prolonged and increased doses of anthracyclines effect QoL and rehabilitation post-chemotherapy.

The use of anthracyclines is limited by dose-dependent cardiotoxicity.⁴ The threshold anthracycline level was not exceeded in either group, so it is unlikely that an additional anthracycline cycle might result in a more prominent decline in cardiopulmonary function. But it has not been ruled out that a prolonged and increased dose of anthracyclines and in addition 5-fluorouracil might cause cumulative side effects, which can impair QoL and trainability. Several studies have consistently demonstrated that physical exercise has a positive effect on QoL following cancer diagnosis, including physical and psychological well being, and may thereby be an effective tool to reverse several side effects of cancer treatment with chemotherapy.^{1,2,5,6} Therefore, not only the difference in side effects, but also the adaptive response to a training programme is relevant when comparing treatment regimes. To evaluate this training response a high-intensity physical-strength training programme was initiated.

AIM

The primary objective of this study was to determine the influence of prolonged and increased anthracycline doses and addition of 5FU (5FEC vs 4AC), as determined by adapted guidelines, on QoL and trainability.

A secondary objective was to evaluate the effectiveness of an 18-week training programme on QoL and trainability in breast cancer survivors.

PATIENTS AND METHODS

This study is a subanalysis from a large running study examining the value of an 18-week training programme.⁶ We used a prospective cohort study design, comparing two chemotherapy regimens historically, with a pre- and post-test design, in the Maxima Medical Centre (MMC) teaching hospital in Veldhoven and Eindhoven. This project was performed by the Department of Internal Medicine and Sports Medicine. The project was approved by the Ethics Review Committee of the MMC and informed consent was obtained from all patients. Based on the current national guidelines at the time, the first cohort (group 1) received 4AC (A 60 mg/m², C 600 mg/m²) and after adaptation of the national guidelines the second cohort (group 2) received 5FEC (F 500 mg/m², E 90 mg/m², C 500 mg/m²) adjuvant polychemotherapy.

Both groups completed an 18-week high-intensity physical-strength training programme.^{6,7} Tests were performed at week 0 and week 18. Eligibility criteria included histologically confirmed breast cancer with no indication of recurrent or progressive disease, age between 25 and 70 years, completion of surgical treatment, adjuvant chemotherapy and radiotherapy 6 to 52 weeks before starting the training programme. We excluded subjects who suffered from serious diseases (cardiac failure, COPD, neurological disorders), which limited their physical performance capacity. Outcome measures were changes in QoL (EORTC-QLQ-C30, MFI-20), muscular strength (one-repetition maximum; leg press) and cardiopulmonary function (VO₂max) between baseline and follow-up.

Measurements

Patient characteristics at baseline were documented. Height and weight were measured. Additionally simple measures for body composition were performed and the body mass index (BMI) was calculated. Skin folds at biceps, triceps, subscapular and suprailiac were measured and percentage body fat was determined from body weight and the skin fold measurements using the equation of Durnin and Womersley.⁸

One-repetition maximum (1RM) of the leg press is a test to determine muscular strength.⁹ 1-RM is the maximum amount of weight that can be lifted once. Indirect 1RM values were calculated from the Brzycki equation.¹⁰ 1RM is stated in kilograms in proportion to body weight. The weight a subject was training with during the programme was used for the test, in addition to which the physiotherapist estimated a weight that could be performed at best ten times. This test was performed at the start (week 0) and at the end of the programme (week 18).

A VO₂max test was performed to define the individual aerobic capacity and is a test to determine cardiopulmonary function. The test was performed on a cycle ergometer with a ramp protocol¹¹ under supervision of a sports physician. An oxymeter was used to obtain breath samples and to analyse O₂ and CO₂ concentrations. Patients were instructed to cycle with a pedal frequency of 70 to 80 revolutions/min and encouraged to continue exercise until exhaustion. The test was ended if patients were unable to maintain the required pedalling frequency and when the patient indicated that he/she could not go any further. This test was performed at the start (week 0) and at the end of the programme (week 18).

To determine the effects of the exercise training programme on QoL and on fatigue, two questionnaires were used as effect parameters. Both questionnaires were completed in week 0 and week 18.

The EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire version 2) is a self-reporting QoL questionnaire developed

for use in clinical trials in oncology.¹² It consists of five functional scales regarding physical, role, emotional, cognitive and social function. Secondly it consists of a scale of global health status and QoL. Thirdly a scale regarding symptoms (subdivided into fatigue, emesis and pain). And lastly, the questionnaire contains questions concerning six single items: dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial impact. The MFI questionnaire (Multidimensional Fatigue Inventory) was especially developed to examine fatigue in cancer patients and includes the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation.¹³

Training programme

The 18-week training programme consisted of high-intensity resistance and interval training. To counteract bias resulting from spontaneous recovery after chemotherapy, training started no earlier than six weeks after completing chemotherapy. The patients trained in groups of six to eight persons on specialised resistance training equipment and on bicycle ergometers under the supervision of physical therapists. During the first 12 weeks, patients trained twice a week. The last six weeks, patients trained once a week.^{6,7}

During the training programme patients could participate in a psychological programme, which was followed once a week for a seven-week period.

Statistical analyses

Statistical analyses were performed using the SPSS version 13.0. Patients in both groups were analysed for differences in age, height, weight, fat percentage, BMI and time from last treatment of chemotherapy, using independent samples *t*-tests. Differences between both groups in number of lymph nodes and receiving radiotherapy or not was analysed using the χ^2 tests. Differences in mean scores for VO₂max, 1RM leg press, EORTC-QOL-C30 and MFI between both groups were analysed using independent samples *t*-tests. Paired sample *t*-tests were used to test the significance of changes in the mean scores from baseline (week 0) to post-intervention (week 18). A *p* value <0.05 was used to indicate statistical significance.

The factors number of lymph nodes, addition of radiotherapy and the time between last received chemotherapy and start of the training programme were considered to influence physical capacity. These items were included as covariates in an ANCOVA analysis, but their influence did not seem to change the outcome.

Because of the great inter-patient differences, it was not possible to extrapolate and fill in the missing values. Therefore, the subjects with one or more missing value were left out of the analysis.

RESULTS

Between March 2002 and February 2006, 75 female subjects with breast cancer participated in this study. The first cohort consisted of 25 subjects, treated in the period of March 2002 to January 2005. The second cohort comprised 50 subjects treated in the period of January 2005 to February 2006.

Although the study design did not allow randomisation, baseline characteristics were similar in both groups as illustrated in *table 1*. The factors number of lymph nodes, addition of radiotherapy and the time between last received chemotherapy and start of the training programme were tested as covariates, but their influence did not seem to change the outcome.

After completing the 18-week training programme, both the AC and FEC group showed a significant improvement in muscular strength (one-repetition maximum; leg press) and cardiopulmonary function (VO₂max) between baseline and follow-up (*table 2*). Both groups also showed improvement in QoL (EORTC-QLQ-C30, MFI-20) (*figures 1A, 1B and 2*).

Concerning the EORTC-QLQ-C30, the AC and FEC group showed significant improvements in physical functioning (AC: *p*=0.015, FEC: *p*<0.0001), role functioning (AC: *p*=0.003, FEC: *p*=0.01), social functioning (AC: *p*=0.003, FEC: *p*=0.001) and global health status (AC: *p*=0.01, FEC: *p*=0.001). Furthermore, a reduction in fatigue (AC: *p*=0.025, FEC: *p*<0.0001) was found in both groups and in dyspnoea only in the FEC group (*p*=0.004). All other items, except diarrhoea (AC), cognitive functioning and constipation (FEC), improved, although not significantly (*p*>0.05). Concerning the MFI-20, significant reductions in both groups were found for general fatigue (AC: *p*=0.05,

Table 1. Patients characteristics

	AC (n=25) Mean (± SD)	FEC (n=50) Mean (± SD)	<i>p</i> -value
Age (years)	49.0 (7.8)	49.7 (8.3)	0.8
Height (cm)	166.3 (6.4)	168.2 (6.0)	0.2
Weight (kg)	73.2 (17.5)	72.8 (14.4)	0.9
Fat (%)	36.5 (5.6)	37.2 (4.8)	0.6
BMI (kg/m ²)	26.4 (5.7)	25.7 (4.9)	0.6
Time between chemo-therapy and training (weeks)	23.3 (12.8)	17.1 (8.5)	0.4
Lymph nodes:			0.07
• 0	12	14	
• ≥1	12	35	
• Unknown	1	1	
Radiotherapy:			0.9
• Yes	18	37	
• No	7	13	

Table 2. VO₂max and IRM leg press training results AC versus FEC

	VO ₂ max			p-value**	IRM leg press			p-value**
	Pre-training (ml/min)	Post-training (ml/min)	Change* (%)		Pre-training (kg/kg bodyweight)	Post-training (kg/kg bodyweight)	Change* (%)	
AC (VO ₂ max n=22/ IRM leg press n=23)	1782 (417)	2060 (412)	12.3 (10.6)	<0.0001	122.8 (35.3)	161.5 (43.0)	56.0 (47.2)	<0.0001
FEC (VO ₂ max n=43/ IRM leg press n=43)	1774 (271)	1991 (352)	13.3 (14.8)	<0.0001	136.8 (34.0)	164.3 (40.4)	46.6 (26.2)	<0.0001
P value#	0.9	0.5	0.8		0.1	0.8	0.4	

*The percentage progression made after completing the training programme. **The p values on the vertical row refer to the significance of the trainings effect: post- vs pre-training. #The p values on the horizontal row refer to the significance of the trainings results compared between the two groups: AC vs FEC.

Figure 1A. Mean scores of the EORTC-QoL-C30 AC group

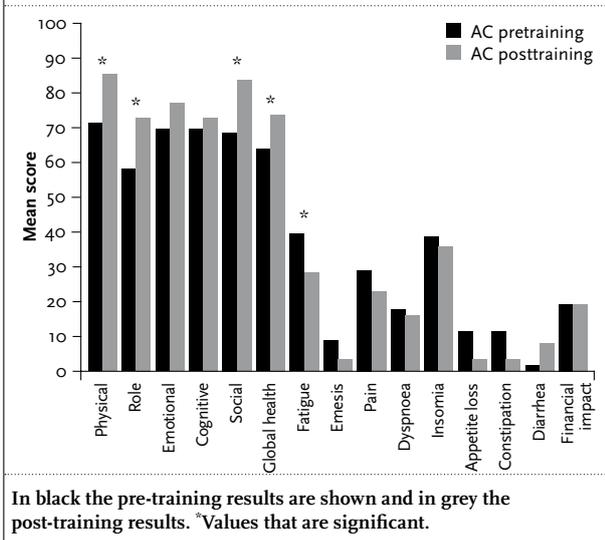


Figure 2. Mean scores of the MFI

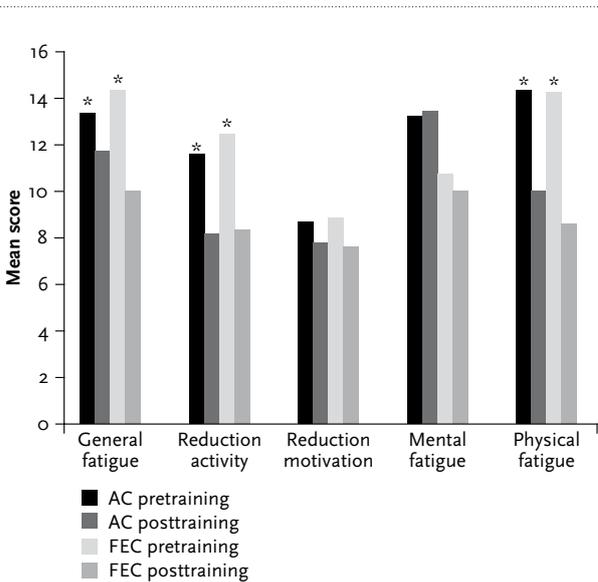
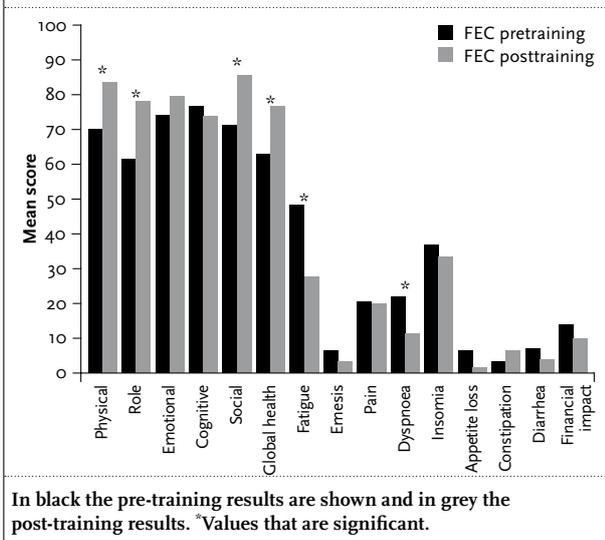


Figure 1B. Mean scores of the EORTC-QoL-C30 FEC group



FEC: $p < 0.0001$), reduction of activity (AC: $p = 0.003$, FEC: $p < 0.0001$) and physical fatigue (AC: $p < 0.0001$, FEC: $p < 0.0001$). The subscale reduction of motivation improved for both groups but not significantly ($p > 0.05$), as well as the subscale mental fatigue for the FEC group. The subscale mental fatigue did not improve post-training in the AC group. When the training response of the two groups was compared, no significant differences in changes of the one repetition maximum of the leg press and the VO₂max were found (table 2); no significant differences in changes of the EORTC-QLQ-C30 and MFI-20 between the two groups were demonstrated either.

DISCUSSION

After adaptation of the national breast cancer treatment guidelines, patients received prolonged and increased doses of anthracyclines. To our knowledge, no studies have been carried out comparing the effect of 4AC vs 5FEC on trainability and QoL. It could be anticipated that addition of an extra anthracycline cycle (5FEC) and the addition of 5-fluorouracil might result in more cumulative side effects, hence worsening the outcome measurements. We did not, however, observe any differences in training response or in quality of life between the two compared groups. Therefore we conclude that the adaptation of the national guidelines for treatment of breast cancer based on improved survival, does not significantly alter the trainability of the patient. This is a non-randomised study in which the choice of a specific chemotherapeutic regime was determined by the adaptation of the national breast cancer guideline. For this reason no power analysis in advance was possible; for the number of patients enrolled in our study, we were dependent on the time-related choice of a therapeutic regimen. The second cohort is double the size of the first cohort. This is explained by the fact that accrual in the beginning of the study went slowly and patients were still being treated with an alternative regimen chemotherapy (CMF), so they could not participate in our study. During the second phase of our study two hospitals merged and patients from two locations could participate. This resulted in a faster accrual. Although the numbers are not the same in both groups, the patient characteristics are. In our opinion comparison between the two groups in this way is very well possible. It cannot be ruled out that in a double-blind randomised study with a higher number of patients, a statistical significant difference in trainability and QoL between the two groups might have been found. We did not encounter medical problems during the training programme. Seventy-five patients started and completed the programme. Because of logistic reasons some patients missed one of the testing dates. These patients were left out of the analysis. The exact number of patients used in the analysis is listed in *table 2*.

From a previous pilot study and a long-term follow-up study by Backer *et al.*,^{6,7} it appeared that the cancer rehabilitation programme of the MMC consisting of a combined muscular strength and endurance programme to improve physical capacity in cancer patients shows positive results. Several other studies have reported the effect of an exercise programme after chemotherapy for breast cancer patients, although other outcome measures were used.^{1,14,15} The positive results demonstrated in the studies are improvements on top of spontaneous improvement in the time after chemotherapy. Our study confirms the effect of a training programme in breast cancer patients on physical condition. Although we

did not use a control group who did not follow the training programme, we found significant improvement of trainability and QoL in both patient groups before and after completing the training programme.

QoL is a more difficult parameter, but at the same time the most valuable for the cancer patient. We assume that improvement of muscular strength and cardiopulmonary function in patients will lead to a better performance of daily activities and resumption of their jobs. This has great impact on economic status and social functioning. Schou *et al.* show in their study that women with breast cancer scored significantly lower on emotional, cognitive, and social functioning at time of diagnosis compared with the general female population, and continued to score lower on cognitive and social functioning one year after surgery. Chemotherapy was predictive for poorer role functioning one year after surgery.¹⁶ Earlier studies confirm the positive effect of (weight) training programmes on QoL in breast cancer survivors.¹⁷ Our study confirms the positive effect of a high-intensity physical-strength training programme on QoL.

QoL and fatigue are not only influenced by physical training. Both are multidimensionally defined. In our study the emphasis lies on physical training. Patients were able to participate in a psychological programme. But only a minority made use of this possibility and the percentage of participation in both groups was equal (20% in the AC vs 22% in the FEC group). Nevertheless, results could be positively influenced by participation in this programme. This can be a point of attention in future studies. Future recommendations would also be to outweigh the potential improvement of outcome in terms of survival and QoL during and after chemotherapy in any new adjuvant regime in breast cancer, such as the recent changes in the national breast cancer treatment guidelines of 2008, in which even a higher dose of anthracyclines is advised. As the number of cancer survivors increases, emphasis has to be on long-term effects of QoL as well.

CONCLUSION

After adaptation of the Dutch national breast cancer treatment guidelines in 2005, patients received prolonged and increased doses of anthracyclines. This, however, did not result in a difference in the baseline situation before rehabilitation and in training response nor in quality of life between the two groups. This preliminary survey suggests that this guideline adaptation, based on improved survival, does not substantially alter the trainability of the patient. But further study is required. This study also confirms the importance of post-chemotherapy training as shown by increase in physical exercise capacity with concomitant increases in QoL experienced by the patients.

NOTE

These data were presented as a poster presentation at the European Cancer Congress (ECCO 14) in Barcelona 23-27 September 2007, abstract: 1137. European Journal of Cancer Supplements, Vol. 5 No 4, Page 153.

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