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Quality of life in patients with metastatic breast cancer receiving either docetaxel or sequential methotrexate and 5-fluorouracil. A multicentre randomised phase III trial by the Scandinavian Breast Group

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Abstract

The purpose of this study was to evaluate the effects of two alternative chemotherapy regimes on the quality of life (QoL) of patients with advanced breast cancer. In a multicentre trial, 283 patients were randomised to receive either docetaxel (T) or sequential methotrexate and 5-fluorouracil (MF). QoL was assessed at baseline and before each treatment using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30). Initial compliance in the QoL study was 96% and the overall compliance 82%. QoL data were available for 245 patients (T 130 and 115 MF). Both treatment groups showed some improvement in emotional functioning during treatment, with a significant difference favouring the MF group at treatment cycles 5 and 6. In the T group, the scores on the other functional scales remained stable throughout the first six cycles. There were significant differences favouring the MF group on the social functioning scale at treatment cycle 6 and on the Global QoL scale at treatment cycles 5 and 6. On most symptom and single-item scales there were no statistically significant differences between the groups. However, at baseline, the T patients reported more appetite loss, at treatment cycles 2–4, the MF patients reported more nausea/vomiting, and at treatment cycle 6, the T patients reported more symptoms of fatigue, dyspnoea and insomnia. There were no statistically significant differences between the groups in the mean change scores of the functional and symptom scales. Interindividual variance was, however, larger in the T group. Differences in QoL between the two treatment groups were minor. Hence, given the expectancy of comparable QoL outcomes, the choice of treatment should be made on the basis of the expected clinical effect.

Keywords: Quality of life; Advanced breast cancer; Chemotherapy; Docetaxel; Sequential methotrexate; 5-Fluorouracil

1. Introduction

Chemotherapy improves the quality of life of a substantial proportion of patients in metastatic settings [1]. More aggressive regimens and continuous therapy result in improvements in QoL compared with less dose-

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intensive or interrupted schedules [2]. Improving the quality of life may in future become an increasingly important consideration in the choice of chemotherapy in patients with metastatic disease. Especially when the goal of the therapy is palliation, improving the patient's quality of life (QoL), or even maintaining it at an acceptable level, may become the most important objective. As a consequence, in clinical trials, systematic assessment of QoL is becoming increasingly established.

According to reviews published in 1997, in advanced breast cancer resistant to anthracyclines, no chemotherapy regimen has shown clear superiority [3,4]. Hence, there is no consensus on the choice of the optimal second-line regimen. However, three recent studies comparing docetaxel with alternative regimens have shown docetaxel to be more effective in terms of response rates [5–7], time to progression [5–7] and, in one of these studies, survival [6]. When expectations concerning survival benefits are only modest, it is of utmost importance to monitor carefully the QoL outcome, since it may turn out to be the decisive factor in determining the superiority of one chemotherapy regimen over another. As yet, there are only few reports on QoL from randomised studies using second-line chemotherapy. In addition, little is known about the effects of taxanes on QoL. Evidence from existing reports is inconclusive, mainly because of problems with missing data and non-random attrition [6,7].

This paper describes the QoL findings of a phase III multicentre trial comparing docetaxel (T) at a dose of 100 mg/m^2 every 3 weeks to sequential methotrexate and 5-fluorouracil (MF) given at days 1 and 8 every 3 weeks at dosages of 200 mg/m^2 and 600 mg/m^2, respectively. Eligible to enter the study were patients with advanced breast cancer after anthracycline failure. The somatic effects are reported elsewhere: briefly, the response rate and TTP (time to progression calculated from randomisation date) were significantly better in the docetaxel arm, whilst the toxicity profile was more favourable in the MF arm [5]. In addition to comparing average scores at specific points in time, the two treatments' potential to produce QoL gains was evaluated by comparing the mean changes in QoL scores from baseline. In the present context, quality of life is understood as a multidimensional, dynamic and subjective concept containing the main dimensions of physical state, psychological well being, social relations and functional capacity [8].

2. Patients and methods

2.1. Patients

A total of 283 patients with metastatic breast cancer were randomised into this study between December 1994 and October 1997 from 22 centres in Scandinavia, Estonia and Poland (Fig. 1). One patient in the MF group was later found to have no recurrence and was excluded from all the analyses. To enter the trial the patients were required to have histologically proven breast cancer that had progressed during or after first-line anthracycline treatment for advanced disease or relapsed within 12 months after discontinuation of adjuvant anthracycline therapy. The patients were required to be $\geqslant 18$ and $\leqslant 70$ years old with a WHO performance score $\leqslant 2$ and with normal values of white blood cells (WBC) ($\geqslant 3\times10^9$/l), platelets ($\geqslant 100\times10^9$/l), serum bilirubin and serum creatinine. Patients were ineligible if they had more than one previous chemotherapy regimen for advanced disease (multiple endocrine treatments and radiotherapy were allowed), prior treatment with taxanes, any concurrent serious medical illness, cerebral or leptomeningeal metastases or history of other malignancies except contralateral breast cancer, basal carcinoma of the skin or *in situ* cervical cancer. Oral and written informed consent was mandatory for both the trial and the QoL measurement. The study was approved by the ethical committees with jurisdiction for the participating centres. The participating institutions and principle investigators are listed in the Acknowledgements.

2.2. Methods

Quality of life was assessed by using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 version 2.0). The validated QLQ-C30 questionnaire incorporates five multi-item scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain, nausea/vomiting) and a global QoL scale and six single-item scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The QLQ-C30 has been found to meet requisite standards of validity, reliability and responsiveness [9–12]. In addition to corresponding well to how QoL was conceived in the present study, the QLQ-C30 was the only instrument available with standardised translations into most of the maternal languages of the patients included in the study. Only the Estonian translation was made *ad hoc*.

2.3. Procedure

The protocol for the present study was written in 1994, but the procedure of the QoL measurement is in all essential aspects in accordance with more recent guidelines [13]. QoL data acquisition was integrated into the clinical routine of the patients in order to maximise compliance and minimise error variance due to uncontrollable differences in the timing or in the external conditions of the assessments. The questionnaire was administered at the clinic, whenever possible in a

room where the patient was not disturbed. The responsible study nurse, or failing that, another member of the staff, gave the patient the questionnaire and demonstrated to her the two different answering modes (yes–no, and scales) in order to make sure that the patient understood the task correctly. The patient was asked to answer all the questions by choosing the best alternative available, even if no alternative offered an exact match. Before answering, the patient was informed about the confidentiality of the answers; it was explicitly stated that they would not be shown to the physician in charge of the treatment. When all questions had been answered, the questionnaire was put in a sealed envelope in front of the patient. The envelope was then mailed to the centre responsible for data entry (Helsinki). The responsible study nurses had participated in a one-day training session during which they were given a checklist of how to organise and monitor the QoL measurements.

According to the study protocol, the first, i.e. baseline measurement was made immediately preceding the administration of the first treatment; hence, when filling in the form, the patients were aware of which treatment they would get. During treatment, QoL assessments were made on day 1 of every treatment cycle, before the administration of the treatment. A time window of −4 to +0 days (anchored to the administration of the treatment) was determined for acceptable assessments. QoL data collection was continued as long as the randomised treatments continued.

2.4. Statistical analysis

Following the instructions in the EORTC QLQ-C30 scoring manual, all raw scores were linearly transformed to a 0–100 scale, with higher scores indicating a higher level of functioning or more symptoms. A difference of 10 scale points or more was regarded as clinically significant, as suggested in previous literature [14]. Missing values for single items (0.8% of all items, ranging between 0.3% and 1.4% across the items) were replaced by values calculated as suggested in the QLQ-30 manual [15]. Imputation of missing data due to patient attrition was not carried out.

Mean scores of the two treatment groups on all scales were compared with baseline scores (i.e. first cycle), second, third, fourth, fifth and sixth treatment cycles.

In order to evaluate the potential QoL gains offered by the two alternative treatments, mean change scores were calculated for those patients who on any given scale had at least one measurement after baseline. The mean change scores were chosen as an additional outcome measure since it was thought that the potential QoL gains offered by the two alternative treatments would be an important clinical consideration in this patient group. These scores also have the advantage of reducing the bias produced by sample attrition, since the results are summarised within each patient. The number of patients who met the criterion of having the baseline assessment and at least one measurement was 214 (117 in the T group and 97 in the MF group). The calculation was made by subtracting the mean score of the cycles 2 to 6 from the patient's baseline score on the same scale.

Statistical software SPSS PC (SPSS Inc, Chicago, IL, USA) for Windows, version 8.0, was used for the statistical analyses. Statistical significance of the differences found between the two treatment arms was tested using the Mann–Whitney U test.

3. Results

The initial compliance was 96% and the overall compliance 89% (percentage received of expected forms). When forms filled outside of the accepted time window (−4 to +0 days) were excluded, the overall compliance of the entire study was 82%. QoL data were available for 245 patients in this analysis: 130 patients in the docetaxel (T) and 115 in the methotrexate and 5-fluorouracil (MF) group. 201 patients were assessable at treatment cycle 2 (105 T and 96 MF), 190 at treatment cycle 3 (104 T and 86 MF), 150 at treatment cycle 4 (86 T and 64 MF), 129 at treatment cycle 5 (80 T and 49 MF) and 106 at treatment cycle 6 (66 T and 40 MF). Reasons for sample attrition are listed in Table 1. Arguably, since the number of patients who discontinued treatment before the sixth cycle because of physical deterioration was greater in the MF group, the results presented below are biased against the T group.

Mean scores for the functional scales and the global QoL scale are shown in Fig. 2. There were no statistically significant differences between the two treatment groups at baseline, nor at the second, third and fourth treatment cycles on any functional scale. During treatment,

Table 1
Reasons for patient attrition at treatment cycle 6

	T	MF
QoL questionnaires received	66	40
QoL protocol violation	13	12
Treatment discontinued due to		
Progressive disease	36	74
Death	6	5
Adverse event	8	2
Patient refusal	9	3
Other	3	3
Missing	1	1
Total attrition due to treatment discontinuation	63	88

T, docetaxel; MF, methotrexate and 5-fluorouracil; QoL, quality of life.

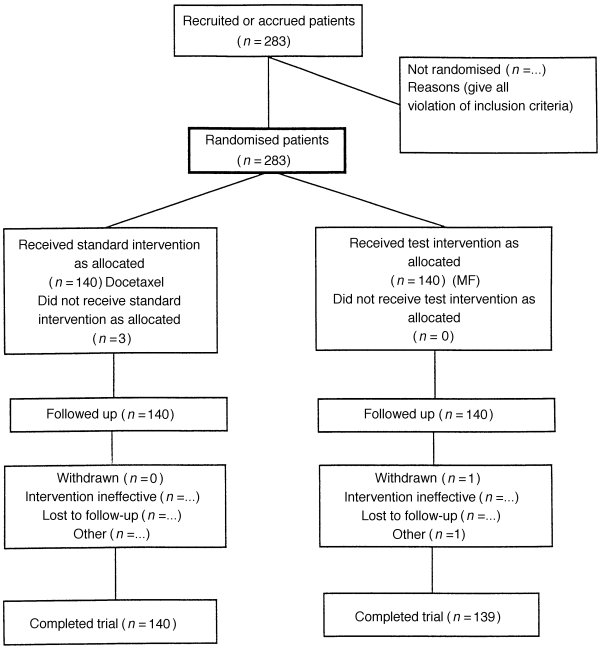

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639). MF, methotrexate and 5-fluorouracil.

the emotional functioning scores of the two groups differed at cycle 5 (T 73.6±SEM 2.5 versus MF 81.6±SEM 3.0; $P=0.028$) and cycle 6 (T 72.9±SEM 2.9 versus MF 86.3±SEM 2.9; $P=0.002$). Mean scores for the social functioning scale in both treatment groups remained stable until, at treatment cycle 6, the MF scores increased, leading to a significant group difference (T 68.7±SEM 3.0 and MF 78.3±SEM 3.9; $P=0.031$). Mean scores for physical, role and cognitive functioning did not change much over time in either group, and there were no significant differences between the groups. The global QoL scale scores remained relatively stable in the MF group and decreased in the T group during treatment. The difference in mean scores was significant from treatment cycle 5 to treatment cycle 6: cycle 5 (T 52.2±SEM 2.3 versus MF 64.4±SEM 3.3; $P=0.004$) and cycle 6 (T 49.1±SEM 2.2 versus MF 63.5±SEM 4.0; $P=0.001$).

Mean scores for the symptom scales and single symptom items are listed in Table 2. At baseline, the T patients suffered significantly more from appetite loss (T 24.3±SEM 2.6 versus MF 15.9±SEM 2.3; $P=0.02$). MF patients reported more nausea/vomiting at treatment cycles 2 (T 8.3±SEM 1.8 versus MF 12.8±SEM 2.0; $P=0.013$), 3 (T 6.3±SEM 1.5 versus MF 12.0±SEM

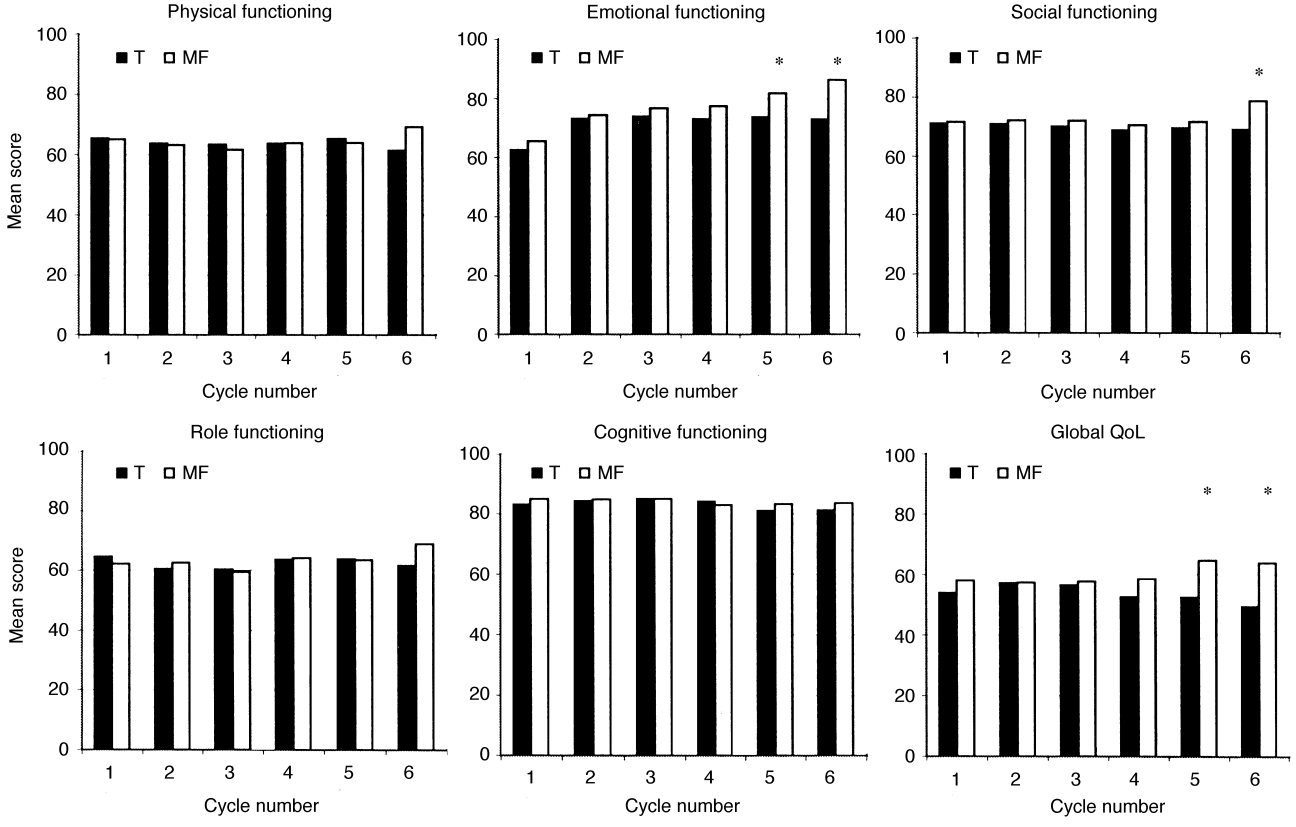

Fig. 2. Functional scale mean scores by treatment group from baseline to sixth treatment cycle. *For statistically significant difference between the two treatment groups ($P<0.05$). Higher scores indicate higher functioning or better global QoL (scale 0–100).

Table 2
Symptom/single item QoL mean scores by treatment group from baseline to sixth treatment cycles

	Baseline		Treatment cycle 2		Treatment cycle 3		Treatment cycle 4		Treatment cycle 5		Treatment cycle 6	
	T ($n=130$)	MF ($n=115$)	T ($n=105$)	MF ($n=96$)	T ($n=104$)	MF ($n=86$)	T ($n=86$)	MF ($n=64$)	T ($n=80$)	MF ($n=49$)	T ($n=66$)	MF ($n=40$)
Fatigue	40.0	40.1	39.9	45.0	39.6	44.6	41.3	43.4	41.0	39.8	43.6	34.2
Nausea/vomiting	10.6	7.4	8.3	12.8	6.3	12.0	4.3	11.4	5.4	6.9	5.6	7.0
Pain	33.9	38.2	23.9	28.5	24.7	25.4	19.2	26.3	23.6	24.2	23.9	20.4
Dyspnoea	24.8	28.7	26.4	23.6	24.9	24.4	29.8	27.0	30.4	28.4	33.3	22.5
Insomnia	31.5	29.8	28.3	23.1	21.5	21.7	24.8	20.8	24.0	23.2	25.3	15.8
Appetite loss	24.3	15.9	17.1	21.2	18.3	25.2	17.4	16.7	15.4	16.5	15.6	13.3
Constipation	13.6	16.2	14.8	20.5	12.8	15.1	14.3	15.9	8.8	10.7	8.1	8.3
Diarrhoea	10.2	6.5	15.4	13.9	11.6	18.2	15.1	19.0	18.3	18.1	19.7	22.5
Financial difficulties	27.6	20.4	28.6	25.0	31.1	24.0	29.1	23.4	29.5	27.3	33.3	24.1

QoL, quality of life; T, docetaxel; MF, methotrexate and 5-fluorouracil.
*For statistically significant difference between the two treatment groups ($P<0.05$). Higher score indicates more symptoms or problems (scale: 0–100).

1.9; $P=0.002$) and 4 (T 4.3±SEM 1.1 versus MF 11.4±SEM 2.1; $P=0.002$). At treatment cycle 6, the T group suffered more from the following symptoms: fatigue (T 43.6±SEM 2.8 versus MF 34.2±SEM 3.6; $P=0.04$), dyspnoea (T 33.3±SEM 3.3 versus MF 22.5± SEM 4.5; $P=0.017$) and insomnia (T 25.3±SEM 3.1 versus MF 15.7±SEM 3.9; $P=0.04$).

Fig. 3 shows the median values of mean changes by treatment group. There were no significant differences between the mean change scores between the groups. However, as shown by the confidence intervals, inter-individual variability was considerably larger in the T group.

4. Discussion

In both treatment groups, little change in QoL occurred between baseline and the fourth treatment cycle. Only in emotional functioning, was there an improvement in both groups, with a significant difference favouring the MF group emerging at treatment cycle 5. During the total period of observation, the scores on all functional scales remained stable in the T group. In the MF group, an increase of the scores on the social functioning scale produced a significant difference between the groups at treatment cycle 6. On the global QoL scale, the difference between the treatment groups emerged at treatment cycle 5 and lasted through treatment cycle 6, favouring the MF group. On most symptom and single-item scales there were no statistically significant differences between the groups. However, at baseline, the T patients reported more appetite loss, at treatment cycles 2–4, the MF patients reported more nausea/vomiting, and at treatment cycle 6, the T patients reported more symptoms of fatigue, dyspnoea and insomnia. These differences correspond well to the different toxicity profiles of the two treatments. MF is associated with somewhat more nausea and vomiting than docetaxel, whilst docetaxel causes more cumulative side-effects such as fluid retention and neuropathy. When mean change scores of functional and symptom scales were used to compare the groups, all statistically significant differences between the groups disappeared. However, the larger variance of change scores in the T group suggests that in this group, the treatment's potential to produce QoL gains was more dependent on individual background variables than in the MF group. On the basis of the present data, it is not possible to speculate on what these variables might be.

In a large international multicentre trial in which the QoL study is optional, some missing data are unavoidable. However, the overall compliance (82%) of the present study is amongst the highest reported in the literature. The baseline scores of both treatment groups

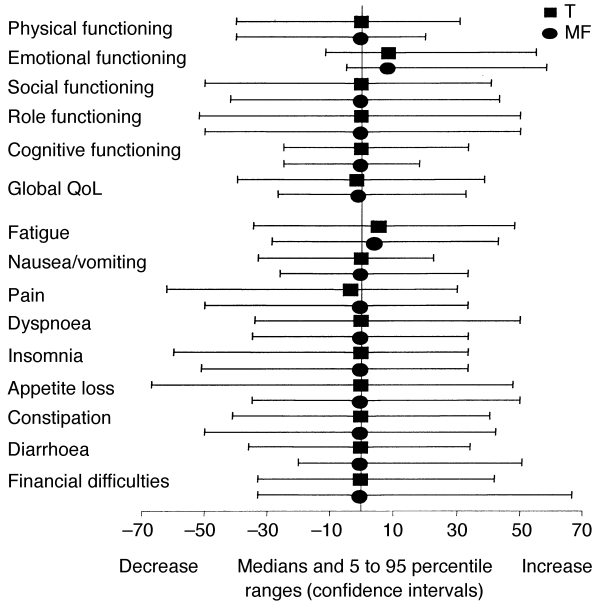

Fig. 3. Median values of mean changes in QoL scores from baseline to sixth treatment cycle by treatment group (n: T = 117, MF = 96). T, docetaxel; MF, methotrexate and 5-fluorouracil; QoL, quality of life.

showed QoL profiles similar to the reference values (data not shown) for advanced breast cancer reported for the EORTC QLQ-C30 [16]. Hence, the present QoL data can be regarded as consistent and clinically plausible. They are also in harmony with earlier results reported from comparable studies concluding that there are no major differences in QoL outcome between docetaxel and alternative regimens [6,7].

All longitudinal studies, particularly in palliative settings where survival may be relatively short, are nevertheless subject to the difficulties of interpretation because of selective attrition of the studied patient populations [9,17,18]. The increasing number of non-random dropouts with time complicates the analysis and interpretations of longitudinal data [19]. This applies to the present findings, too. As seen in Table 1, attrition due to disease progression was larger in the MF group. Consequently, the MF patients remaining in the study through treatment cycle 6 were more a select and less representative subgroup of the baseline study population than the patients remaining in the T group. One way of handling the problem of selective dropout in group comparisons is to use variables summarised within individuals, such as mean change scores. In the present study, all statistically significant differences favouring the MF group disappeared when comparing change scores over treatment rather than group means at specific points in time.

To summarise, the present QoL findings show no major advantage for either treatment over the other. Despite more pronounced side-effects (as documented by Sjöström and colleagues [5]), the T patients experienced relatively stable quality of life during treatment. This is a valuable outcome in a palliative setting, especially when taking into account the superiority of the T treatment over alternative treatments in terms of time to progression and response rate [5–7] and of survival [6]. It is also of interest to note that both treatments were able to improve the quality of life of some patients significantly. However, since there was large inter-individual variance, especially in the T group, further studies are needed to understand better how variation during treatment in quality of life is related to patient characteristics, response and toxicity.

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