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Prognostic value of quality of life scores for time to progression (TTP) and overall survival time (OS) in advanced breast cancer

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Abstract

The purpose of the study was to investigate whether baseline quality of life (QoL) and changes in QoL scores from baseline are prognostic for time to progression (TTP) and/or overall survival (OS) in patients with advanced breast cancer receiving 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). Survival curves and probabilities were estimated using the Kaplan–Meier technique. The Cox proportional hazards regression model was used for both the univariate and multivariate analyses to explore relationships between baseline QoL variables and TTP, as well as OS. In the univariate analysis, more severe pain and fatigue at baseline were predictive for a shorter OS; global QoL, physical functioning and appetite loss had a borderline significance ($P=0.0130$ for global QoL; $P=0.0256$ for physical functioning: $P=0.0149$ for appetite loss). World Health Organization (WHO) performance status was significantly predictive for OS. In the multivariate analysis, more severe pain at baseline was predictive for a shorter OS. In contrast, baseline QoL had no prognostic value for the duration of TTP. QoL change scores from baseline QoL predicted neither OS nor TTP. Our findings suggest that while QoL measurements are important in evaluating patients' QoL, they have no great importance in predicting primary clinical endpoints such as TTP or OS in advanced breast cancer patients.

Keywords: Quality of Life; Advanced Breast Cancer; Prognostic value; Time to progression; Overall survival; Docetaxel; Methotrexate; 5-Fluorouracil

1. Introduction

In many clinical trials with advanced cancer, the efficacy of treatment is evaluated by assessing treatment response and survival. However, there has been a growing consensus among researchers that the efficacy of therapeutic interventions should be evaluated by their impact on both quantity and quality of life (QoL). Consequently, QoL has become an important secondary endpoint in clinical trials. There are several valid and reliable QoL instruments to measure changes in QoL caused by disease or treatment. QoL data can be used to enhance physicians' and patients' decision-making by

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providing information on the physical, emotional and social effects of treatment. Although the focus of QoL research has been on comparing patients' QoL between different treatments, recently, several studies have suggested that QoL may also have an independent prognostic value and can predict survival [1–10].

The association between QoL and survival has been noted in patients with advanced breast cancer [5,9,11–13]. Only a few studies have investigated the prognostic impact of QoL as measured by the European Organization for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire (EORTC) QLQ-C30 [9]. They suggest that dyspnoea, fatigue and poor global QoL are predictive for a poor treatment response.

In randomised clinical chemotherapy trials, the time to progression (TTP) is an important endpoint, especially in cross-over studies, in which no substantial difference in survival is expected. However, to our knowledge, there are no previous studies examining whether baseline (i.e. pretreatment) QoL scores or changes in QoL scores have a predictive value for TTP.

The purpose of the present study was to investigate whether baseline QoL and/or changes in QoL scores from baseline are prognostic for TTP in patients with advanced breast cancer receiving either docetaxel (T) or sequential methotrexate and 5-fluorouracil (MF). As this study was a cross-over study, there was no significant difference in OS between the two treatment groups. Therefore, we found it interesting to examine whether baseline QoL and/or changes in QoL scores had a prognostic value in this patient population.

Because the World Health Organization (WHO) performance status, as assessed by a physician, is widely used and has a prognostic value for TTP [14], we also wanted to investigate whether QoL variables have an independent prognostic value for TTP and/or overall survival (OS).

2. Patients and methods

The present trial was a randomised phase III study comparing T with sequential MF. After relapse, cross-over to the alternative treatment group was recommended (MF for patients treated with T and T for patients treated with MF). The primary endpoint was TTP measured from the date of randomisation until tumour progression or death or last follow-up visit. Response rates, toxicity, OS and QoL were secondary endpoints. OS was measured from the date of randomisation until death. The clinical findings of the trial have been reported elsewhere in Ref. [14]: Briefly, median TTP was significantly longer in the T group (6.3 months versus 3.0 months in the MF group: range 2 days to 19 months) and the response rate was significantly better in the T arm, while the toxicity profile was more favourable in the MF arm. The median overall survival did not differ significantly (10.4 months in the T group and 11.4 in the MF group: range 6 days to 29 months). The QoL findings have also been reported elsewhere in Ref. [15]; there were no major differences in QoL between the treatment groups.

2.1. Patients

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 18–70 years old with a 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 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 malignancy 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 for the participating centres. The participating institutions and principal 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 consists of five function scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain and 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 [16–19].

The following QoL-variables were studied: global QoL, all functional scales; fatigue, pain, insomnia, dyspnoea and appetite loss. We excluded constipation, diarrhoea and nausea/vomiting scales because they measure toxicity of the treatment rather than symptoms of the disease. We also excluded the financial difficulties item because we could not understand why that item should predict TTP or OS.

EORTC QLQ-C30 raw scores were calculated according to guidelines, yielding a range of 0–100. Higher scores indicating a higher level of functioning and better global QoL or more symptoms. All baseline

QoL variables were dichotomised at the median to yield 'good' or 'poor' scores.

We also calculated change scores indicating a change in QoL between baseline (i.e. first measurement) and the third treatment course. The third course was selected because patients had experience from the treatment and attrition from the study was minimal. This procedure ensured the most representative samples in both treatment arms. The change data was available for 173 patients. In order to reduce bias from extreme baseline scores (i.e. 0 or 100), the cases scoring 0 or 100 at baseline were omitted from analysis. The percentage of cases omitted from the analysis for that reason depended on the variable and varied from 11% for social functioning to 45% for role functioning, with a mean of 36%.

In addition to the administration of the EORTC QLQ-C30, WHO performance status was used to rate patients' physical performance. It is a five-grade physician rating of patients' physical ability ranging from normal to 100% bedridden. In these data, the baseline WHO performance score ranged from 0 (normal activity) to 2 (in bed $<50\%$ of waking time).

2.3. Statistics

Survival curves and probabilities were estimated using the Kaplan–Meier technique. The Cox proportional hazards regression model was used for both the univariate and multivariate analyses to explore the relationship between baseline QoL variables and TTP, as well as OS. For multivariate analysis, Cox regression analysis was performed using a stepwise method and both forward and backward procedures were performed. Both methods yielded same results. The importance of single prognostic factors was assessed using the P value of the Wald X2 statistics, the hazard ratio and its 95% confidence interval (CI) for TTP and OS. Differences in TTP and OS were tested by the log-rank test.

To explore the relationship between the change in QoL variables and TTP, as well as OS, the Cox proportional hazards regression model was used for the univariate analysis. From those analyses, we excluded the patients who scored 100 or 0 at baseline (since in these patients, QOL could change in only one direction).

To reduce the risk of false-positive results arising from multiple testing, a significance level of 1% was chosen.

3. Results

A total of 283 patients with metastatic breast cancer were randomised into this study between December

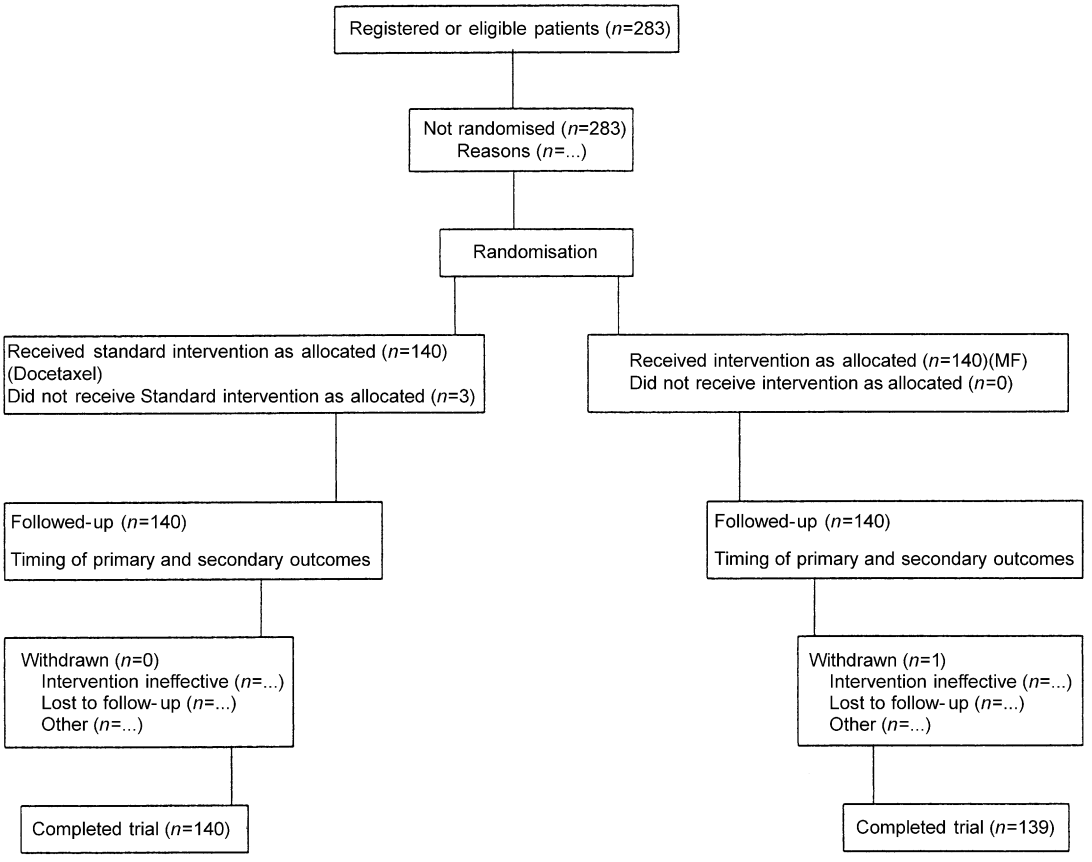


Fig. 1. Progress through the various stages of a trial, including flow of participants, withdrawals, and timing of primary and secondary outcome measures.

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 recurrences and was excluded from all of the analyses. The compliance of the baseline QoL measurement (percentage received of expected forms) was 96%. Further details are provided in our paper reporting the overall QoL findings [15,20]. Mean baseline QoL scores are shown in Table 1.

Table 2 lists the results of the univariate survival analyses for each QoL variable. None of the patient-rated QoL variables were significantly predictive for TTP.

However, the WHO performance status was significantly predictive for TTP duration: patients with a performance status of 2 had a significantly shorter TTP than patients with a performance status of 0 or 1 (Fig. 2).

Shorter OS was associated with more severe pain and fatigue (Table 3).

The WHO performance status was associated with OS. Patients who had a WHO performance score of 0–1 lived significantly longer than patients with a WHO performance score of 2. Fig. 3 shows survival according to the baseline WHO performance score.

The Cox multivariate regression model showed that more severe pain was associated a with shorter overall survival (Table 4). Changes in QoL between baseline and third treatment course had no prognostic value either for TTP or for OS.

4. Discussion

In the present study, we found that in univariate analysis, more severe pain and fatigue at baseline were predictive for a shorter OS, whereas global QoL, physical functioning and appetite loss had a borderline significance ($P=0.0130$ for global QoL; $P=0.026$ for physical functioning: $P=0.0149$ for appetite loss). In the multivariate analysis, more severe pain at baseline was an independent predictor for a shorter OS. In contrast, baseline QoL had no prognostic value for TTP. However, the WHO performance score was associated with TTP. QoL change scores from baseline predicted neither OS nor TTP.

Several studies have shown pre-treatment scores of QoL to be predictive for survival in different cancer patient populations. In multivariate analysis, the following QLQ-C30 variables have been associated with OS: cognitive functioning [21], physical functioning [7,10], social functioning [5]; global QOL [5,8,13] and pain [9]. In univariate analysis, in addition to these QLQ-C30 variables, role functioning [5,7,13], emotional functioning [5], fatigue [5,7–10,13,21], dyspnoea, appetite loss and constipation [13] have shown prognostic value for OS. In patients with metastatic breast cancer,

Table 1
Baseline QoL scores[a]

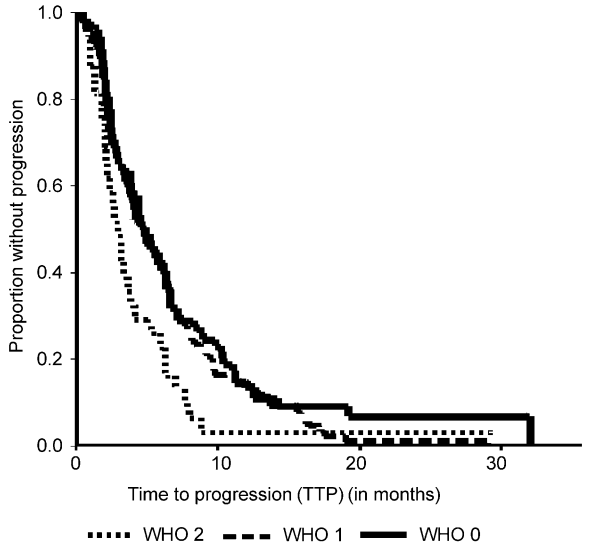
	n	Mean	Median	S.D.
Global QoL	243	55.8	50.0	23.1
Physical	244	65.2	60.0	27.1
Emotional	242	64.0	66.7	24.6
Social	243	71.2	83.3	29.1
Cognitive	242	83.9	83.3	19.9
Role	244	63.3	50.0	33.6
Fatigue	242	40.1	33.3	27.3
Pain	243	35.6	33.3	30.2
Insomnia	243	31.0	33.3	30.7
Appetite loss	241	20.5	0.0	27.8
Dyspnoea	241	26.8	33.3	30.2

QoL, quality of life; S.D., standard deviation.
[a] A high score reflects a high level of symptons or functioning or global QoL.

Table 2
Univariate prognostic factor analysis for TTP

Variable	*n*	Median TTP (months)	Hazard ratio (95% confidence interval)	*P* value
Global QoL				
>50 good	119	4.9		
⩽50 poor	124	4.1	1.13 (0.86–1.47)	0.379
Physical				
>60 good	109	4.6		
⩽60 poor	135	4.2	1.14 (0.78–1.50)	0.328
Emotional				
>67 good	107	4.8		
⩽67 poor	135	4.2	0.90 (0.70–1.19)	0.487
Social				
>83 good	85	4.2		
⩽83 poor	158	4.6	0.10 (0.75–1.30)	0.940
Cognitive				
>83 good	116	4.2		
⩽83 poor	126	4.6	1.10 (0.83–1.42)	0.562
Role				
>50 good	96	5.0		
⩽50 poor	148	3.8	1.10 (0.83–1.43)	0.536
Fatigue				
⩽33 good	139	4.8		
<>33 poor	103	3.8	1.24 (0.10–1.62)	0.120
Pain				
⩽33 good	158	5.1		
>33 poor	85	3.8	1.22 (0.92–1.62)	0.164
Insomnia				
⩽33 good	176	4.2		
>33 poor	67	4.9	0.92 (0.68–1.24)	0.603
Appetite loss				
⩽0 good	136	4.6		
>0 poor	105	3.9	0.10 (0.74–1.27)	0.814
Dyspnoea				
⩽33 good	193	4.4		
>33 poor	48	4.2	0.10 (0.685–1.36)	0.835

TTP, time to progression.



Variable	n	Median TTP (months)	P value (bw 0&2)	P value (bw 1&2)
WHO 0	72	5.0	0.0092	
WHO 1	140	4.8		0.029
WHO 2	32	3.0		

Fig. 2. Duration of time to progression (TTP) by World Health Organization (WHO) physical performance score (0 versus 1 and 0 versus 2). bw, between.

better pre-treatment mood, appetite, physical well-being, coping [22], and overall QoL [12] have been associated with a longer survival. The findings of our study do not support these earlier findings. One reason for this might be the different QoL questionnaire; Coates and colleagues used the Linear Analogue Self Assessment (LASA) scale, while we used the QLQ-C30.

The univariate findings of the present study suggest that baseline QoL has a prognostic value for OS in advanced breast cancer patients. However, the findings differ from earlier studies. Kramer and colleagues [9] reported that pain, global QoL, and fatigue (using QLQ-C30) were significant prognostic factors in univariate analysis, but only pain remained significant in multivariate analysis. In our study, pain and fatigue were strongly predictive for OS, while global QoL, physical functioning, and appetite loss had a borderline significance. In the multivariate model, pain predicted a shorter survival which supports the findings of Karmer and colleagues [9] (2001) finding that pain is an important prognostic factor for survival in advanced breast cancer patients. In Butow's [23] study on advanced breast cancer patients, better appetite predicted a shorter survival which again is contradictory to our findings. Again, they used a different QoL questionnaire.

There has been some evidence that change scores from baseline QoL can predict overall survival. In Blazeby's study [10], improvements in emotional functioning were significantly associated with a longer survival in 38 patients. In another study with 64 advanced breast cancer patients, change scores in physical well-being, mood, pain, and overall QoL were predictive for a longer overall survival [12]. It is difficult to generalise from these studies because the number of patients alive in both studies was reduced. In our study, we selected the third treatment course as the change value from baseline in order reduce bias produced by selective drop-out (due to different sample attrition between the treatment arms). In contrast to earlier studies, the results of our study, based on 173 patients, suggest that change from baseline QoL does not predict either OS or TTP.

The compliance of the present study was exceptionally high (96%) and data were of a very high quality; the timing of the measurements was controlled in order to reduce bias induced by inadequate timing [24]. Therefore, we

Table 3
Univariate prognostic factor analysis for OS

Variable	n	Median OS (months)	Hazard ratio (95% confidence interval)	P value*
Global QoL				
>50 good	119	14.8		
⩽50 poor	124	9.6	1.39 (1.07–1.82)	0.0130
Physical				
>60 good	109	13.3		
⩽60 poor	135	9.9	1.35 (1.04–1.77)	0.0256
Emotional				
>67 good	107	12.8		
⩽67 poor	135	10.4	1.14 (0.88–1.50)	0.3206
Social				
>83 good	85	13.2		
⩽83 poor	158	10.4	1.16 (0.87–1.53)	0.3083
Cognitive				
>83 good	116	13.3		
⩽83 poor	126	9.7	1.24 (0.948–1.62)	0.1165
Role				
>50 good	96	15.2		
⩽50 poor	148	9.9	1.33 (1.01–1.74)	0.042
Fatigue				
⩽33 good	139	14.5		
>33 poor	103	8.6	1.48 (1.129–1.93)	**0.0044**
Pain				
⩽33 good	158	12.9		
>33 poor	85	8.5	1.46 (1.10–1.94)	**0.008**
Insomnia				
⩽33 good	176	12.0		
>33 poor	67	10.2	1.11 (0.83–1.48)	0.486
Appetite loss				
⩽0 good	136	13.2		
>0 poor	105	9.9	1.40 (1.07–1.83)	0.0149
Dyspnoea				
⩽33 good	193	11.9		
>33 poor	48	10.4	0.96 (0.68–1.35)	0.8091

*Bolded *P* values are significant.

Table 4
Multivariate Cox regression model for prognostic factors on overall survival

Variable	B	S.E.	Wald	df	Sig.	RH	95% CI for RH	
							Lower	Upper
Fatigue	0.0007	0.00382	0.03782	1	0.8457	1.000	0.993	1.008
Global QoL	−0.0017	0.00406	0.19334	1	0.6601	0.998	0.990	1.006
Role functioning	0.0018	0.00286	0.42518	1	0.5143	1.002	0.996	1.008
Physical functioning	−0.0021	0.00336	0.40535	1	0.5243	0.998	0.991	1.004
WHO performance status	0.1271	0.12567	1.02360	1	0.3116	1.135	0.887	1.452
Appetite loss	0.0044	0.00252	3.12685	1	0.0770	1.004	0.999	1.009
Pain	0.0072	0.00234	9.56787	1	**0.0020**	1.007	1.003	1.012

RH, relative hazard; df, degrees of freedom; S.E., standard error; CI, confidence Interval; Sig., significance.

can see no methodological reason to question the findings of the present study although it fails to replicate earlier positive findings concerning the predictive power of QoL. In the absence of other published negative findings, we find it useless to speculate on the underlying causes of this discrepancy.

In conclusion, our findings suggest that while QoL measurements are important in evaluating patients' QoL, they do not have a great importance in predicting primary clinical endpoints such as TTP or OS. However, the results of this study confirm pain has a prognostic significance for survival in advanced breast cancer patients. It would be interesting to study the predictive value of pain for survival as measured by clinicians and as reported by patients.

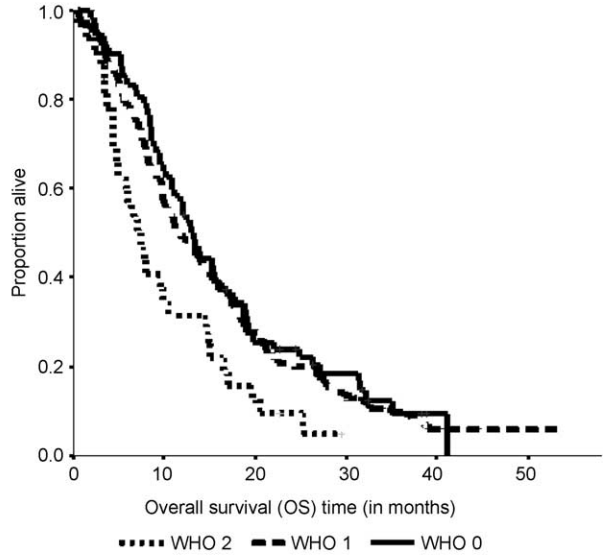


Fig. 3. Duration of overall survival (OS) by World Health Organization (WHO) physical performance score (0 versus 1 and 0 versus 2). bw, between.

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