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Original Paper

Psychological Factors can Predict the Response to Primary Chemotherapy in Patients with Locally Advanced Breast Cancer

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This study evaluated the possible value of psychological variables in predicting clinical and pathological response to primary chemotherapy. 96 women with newly diagnosed large, or locally advanced, breast cancer (T_2>4 cm, T_3, T_4, N_2 and M_0) participated in a prospective, randomised trial to evaluate the effects of relaxation training with guided imagery and L-arginine on response to primary chemotherapy. Before the first of six cycles of primary chemotherapy, women were assessed using the Hospital Anxiety and Depression Scale (HADS) and the Eysenck Personality Questionnaire (EPQ). The primary outcomes were clinical response (evaluated using standard International Union Against Cancer (UICC) criteria) and pathological response (graded by means of a previously published 5-point scale) following primary chemotherapy. Stepwise linear regressions were used to estimate the predictive value of age, menopausal status, clinical nodal status, tumour size at diagnosis, oestrogen receptor status, dietary supplementation (L-arginine versus placebo), personality (EPQ-L scores), mood (HADS scores) and a psychological intervention. HADS depression score was a significant independent predictor of pathological response to chemotherapy. HADS anxiety score was a significant independent predictor of clinical response. Because the original tumour size before chemotherapy (also a significant predictor of clinical and pathological responses) was taken into account in the analyses, the results cannot be explained in terms of psychobiological factors related to tumour size. This study supports the importance of psychological factors as independent predictors of response to primary chemotherapy in patients with breast cancer. If they can be replicated, these findings have major implications for the management of women with breast cancer. Psychological factors need to be assessed and evaluated in future trials of chemotherapy. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

Up to 25% of women with breast cancer have large or locally advanced disease at initial presentation [1, 2]. If these patients are treated with surgery alone, 5-year survival is poor and almost half of those with locally advanced disease will have failure of local control of disease [3]. Most deaths are due to disseminated disease, which is present as occult micrometastases at the initial presentation.

To improve local control and survival of these patients, primary chemotherapy may be used with a view to down-staging the breast tumour and reducing, or eliminating, micrometastatic disease [4–8]. The clinical response rates (standard International Union Against Cancer (UICC) criteria) to such treatment range from less than 50% to more than 90% [2, 9]. The clinical and pathological responses are important determinants of survival following the completion

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of chemotherapy [4, 10–12]. However, primary chemotherapy is frequently accompanied by significant physical and psychological morbidity. Consequently, in some studies, patient compliance has been poor [13].

It would be advantageous, therefore, to predict which patients are most likely to demonstrate a clinical or pathological response to primary chemotherapy. Established biological predictors are the size of the tumour, the nodal status, oestrogen receptor (ER) status and the presence of metastatic disease at presentation. However, psychological factors may also be important determinants in survival in patients with cancer [14]. For example, good quality of life scores are associated with prolonged survival in patients with advanced cancers [15–19]. Moreover, in patients with advanced breast cancer who underwent adjuvant chemotherapy, good quality of life scores before treatment predicted a better response to chemotherapy [17, 20, 21].

Other psychological factors have also been examined to determine if these may be important in patients with malignant disease undergoing chemotherapy [22]. In a randomised study of 63 patients with lymphoma who received chemotherapy [22] we found that not receiving a psychological intervention, high depression scores on the Hospital Anxiety and Depression Scale (HADS) [23] and high L-scores on the Eysenck Personality Inventory (EPI) [24] at diagnosis were independent prognostic factors for death within 5 years (the L-score detects dissimulation and also measures some stable personality factor that may denote social naïveté or excessive conformity) [24]. To the best of our knowledge, the extent to which psychological factors predict clinical and pathological responses to primary chemotherapy has not been studied.

We recently reported a study of the effects of a psychological intervention (relaxation and guided imagery) and dietary supplementation (L-arginine) in women receiving neoadjuvant chemotherapy for large or locally advanced breast cancer [25, 26]. This dataset provided the opportunity to determine the extent to which psychological factors could predict clinical and pathological responses to primary chemotherapy. Our lymphoma study [22] prompted us to postulate that depression scores, L-scores and the psychological intervention would be independent prognostic factors for response to chemotherapy.

PATIENTS AND METHODS

Patients

The main inclusion criteria for the study were: large or locally advanced breast cancer (T_2>4 cm, T_3, T_4, N_2 and M_0); under 75 years of age, medically suitable for neoadjuvant chemotherapy and World Health Organisation (WHO) performance status 0 or 1 [27]. All patients underwent bilateral mammography, ultrasound imaging of the breast lesion, fine needle aspiration cytology and/or core biopsy of the tumour. Staging investigations were: serum biochemistry, full blood counts and differentials, plain radiographs of chest, pelvis and lumbar spine, isotope bone scans, and abdominal ultrasound (if liver function tests were abnormal).

The Joint Ethical Committee of Grampian Health Board and the University of Aberdeen approved the study.

Primary chemotherapy

Six cycles of chemotherapy were given at 21-day intervals (cyclophosphamide 1 g/m^2 (maximum dose per cycle: 1.8 g); vincristine 1.5 mg/m^2 (maximum dose per cycle: 2 mg); doxorubicin 50 mg/m^2 (maximum dose per cycle: 90 mg), all given as intravenous bolus injections and followed by prednisolone 40 mg orally for 5 days). The dose of chemotherapy was adjusted according to the white cell count (WCC) and platelet count (Plts) in blood. If the WCC <3.0 and >2.5×10^9/l and/or the Plts was <150 and >75×10^9/l, the dose of cyclophosphamide and doxorubicin was reduced by 25% for all further cycles. If the WCC was <2.5×10^9/l and/or the Plts was <75×10^9/l, chemotherapy was delayed for 1 week and the cyclophosphamide and doxorubicin doses were then reduced by 25% for all subsequent cycles.

Four weeks after the six cycles of chemotherapy, patients underwent surgery. This comprised either mastectomy or quadrantectomy (depending on the response of the tumour and also the patient's preference) and axillary surgery (sample or clearance, at the discretion of the surgeon).

Clinical response to primary chemotherapy

Prior to each cycle of chemotherapy, and prior to surgery, clinical measurements of the tumour, using calibrated skin callipers (four diameters, at 45-degree intervals), were recorded [28]. The final measurement for each patient was used in the analysis. Response rates were classified, using standard UICC criteria, as progression of disease (PD), stable disease (SD), partial response (PR) and complete response (CR) [29]. Clinical responses were determined by documenting the product of the two maximal perpendicular diameters [30].

Pathological responses to primary chemotherapy

Histological responses of excised breast tissue were assessed as previously documented by a consultant breast histopathologist [31]. Briefly, the response to chemotherapy is graded according to the residual tumour found histologically as follows: Type I, changes in tumour cells but tumour nests not destroyed; Type II, tumour structure destroyed to a minor degree; Type III, tumour structure destroyed to a moderate degree; Type IV, tumour structure destroyed to a severe degree; Type V, no tumour cells in any of the specimens.

Psychological assessments

Psychological assessments were undertaken before the commencement of primary chemotherapy, and after informed consent had been obtained and the patients had been randomised as follows: (1) Hospital Anxiety and Depression Scale (HADS): a 14-item self-report questionnaire that measures anxiety and depression [23]; and (2) The Eysenck Personality Questionnaire (EPQ-R): a factorially-derived 106-item scale which measures extroversion, neuroticism, psychoticism and also contains a validity scale (the L-scale) [24].

Setting

The study was carried out in the Behavioural Oncology Unit, which is based in the Professorial Surgical Unit, Aberdeen Royal Infirmary, U.K. Considerable efforts were made to minimise chemotherapy waiting times and patients were normally given chemotherapy by the same physician in a designated, pleasant and private environment. Efforts were made to make patients as comfortable as possible and at ease. Concerns were actively elicited and attempts were made to deal with these as effectively and expeditiously as possible. Patients knew they were welcome to telephone or to come to

the Unit at any time. Although formal group meetings were not held, many patients would arrange to meet their peers in the Unit to discuss issues of common interest and concern. Family members and friends were also welcome.

Interventions

Patients participated in a prospective, randomised, controlled, clinical trial to evaluate the effects of relaxation training (RT) with guided imagery (GI) on quality of life and the clinical and pathological effects of dietary supplementation with L-arginine prior to chemotherapy. A stratified procedure was used to ensure that there were equal numbers of patients in the four combinations of treatment (placebo, RT + GI; L-arginine, RT + GI; placebo, no RT + GI; and L-arginine, no RT + GI).

Relaxation was taught live on five occasions during the 18 weeks of chemotherapy and patients were issued with audio cassette recordings containing instructions for progressive muscular relaxation training and cue-controlled relaxation training. In addition, they were given a portfolio of ten coloured cartoons to help them visualise their host defences destroying the cancer cells. They were asked to practise relaxation and guided imagery at least daily; diary recordings made each day indicated the following compliance: 52% less than daily, 25% 1–1.5 times daily, and 23% more than 1.5 times daily [25]. Patients randomised to dietary supplementation were given 30 g L-arginine daily for 3 days prior to each cycle of chemotherapy. A pilot study had suggested an enhanced response to chemotherapy with prior supplementation with L-arginine [31].

Variables analysed for prognostic significance

The following variables were assessed for their prognostic value: age, menopausal status, tumour size at diagnosis, clinical nodal status, oestrogen receptor (ER) status, dietary supplementation (L-arginine versus placebo), psychological intervention (RT and GI versus control), EPQ-L scores and HADS anxiety and depression scores.

Data analysis

Data were analysed using SPSS MS for Windows. Distributions were screened and transformed to approximate normality ($\log_{10}$ for tumour size, and square root for HADS anxiety). Stepwise linear regressions were carried out using all variables to determine independent prognostic factors [32]. All patients except the 3 who died were included in the analysis on an intention-to-treat basis.

RESULTS

Patients

A consecutive series of 97 patients were invited to participate and 96 gave written informed consent. These 96 patients were randomised using a stratified procedure to balance the experimental and control groups for menopausal status and numbers (24 patients in each group). The patients were aged from 30 to 73 years (median age = 47 years): 51 were premenopausal. There were 74 invasive ductal carcinomas, seven lobular carcinomas and two tubular carcinomas (histological assessment of the tumour was not possible in 10 patients who showed a complete response or in 3 patients who died).

3 patients died, 5 received less than six cycles of chemotherapy, 1 patient had more than six cycles and 1 patient withdrew from the study. To determine if these 10 patients (deviators) differed from the remaining 86 in terms of putative prognostic factors at baseline, the two groups were compared using chi-squared tests and *t*-tests. The two groups did not differ significantly in terms of clinical tumour size at diagnosis ($t = 0.59$, ns), clinical nodal status ($\chi^2 = 0.68$, ns), ER status ($\chi^2 = 3.17$, ns), dietary supplementation (L-arginine versus placebo) ($\chi^2 = 0.00$, ns), psychological treatment (RT and GI versus control) ($\chi^2 = 0.00$, ns), EPQ-L scores ($t = 1.89$, ns) and HADS anxiety ($t = 0.67$, ns) and depression scores ($t = 1.50$, ns). Although the ages of the deviators and non-deviators were similar ($t = 1.66$, ns), a higher proportion of postmenopausal women deviated from the protocol ($\chi^2 = 4.91$, $P = 0.03$).

41 patients received one or more dose reductions. However, dose reduction was not associated with clinical response ($\chi^2 = 2.34$, ns) or with pathological response ($\chi^2 = 0.29$, ns). Similar proportions of patients in the psychological treatment groups ($\chi^2 = 0.00$, ns) and dietary supplementation ($\chi^2 = 0.00$, ns) groups received one or more reduced doses of chemotherapy.

The patient details are shown in Table 1. All patients were followed-up to death or surgery.

Clinical responses

The overall clinical response rate was 73% (70/96) (complete response 19% (18/96), partial response 54% (52/96)); stasis of disease occurred in 24% (23/96) and disease progression in 3% (3/96) of patients. In terms of disease stage, the responses were as follows: 18 CRs—9 T_2, 8 T_3, 1 T_4; 10 N_0, 8 N_1. 52 PRs—1 T_x, 15 T_2, 29 T_3, 7 T_4; 37 N_0, 12 N_1, 3 N_2. 23 SDs—5 T_2, 14 T_3, 4 T_4; 11 N_0, 10 N_1, 2 N_2. 3 PDs—1 T_3, 1 T_4; 3 N_1.

Table 1. *Characteristics of patients entered into the study*

	Patient No.
Mean age (S.D.)	50 (30–73) years
Tumour stage (numbers)	
T_x	1
T_2	29
T_3	52
T_4	14
Clinical nodal status	
N_0	58
N_1	33
N_2	5
Menopausal status	
Premenopausal	51
Postmenopausal	45
HADS scores	
Anxiety	
Mean (S.D.)	6.9 (3.7)
Median (range)	7.0 (0–17)
Depression	
Mean (S.D.)	2.53 (2.4)
Median (range)	2.0 (0–10)
EPQ	
L-scale Mean (S.D.)	11.24 (4.18)

S.D., standard deviation; HADS, Hospital Anxiety and Depression Scale; EPQ, Eysenck Personality Questionnaire.

Table 2. Corrrelations between response and putative prognostic variables

	Correlation coefficients										
	Clinical response	Path. R	Age	MS	TS	ER	DS	PT	EPQ-L	Anx.	Dep.
Clinical response	1.00	−0.46†	−0.06	0.06	0.23*	0.11	0.10	0.16	−0.17	0.32†	0.24*
Pathological response (Path. R)		1.00	0.03	−0.03	−0.29†	0.00	−0.03	−0.10	0.10	−0.26*	−0.37†
Age			1.00	0.79†	−0.04	0.06	0.08	−0.05	0.33†	−0.13	0.04
Menopausal status (MS)				1.00	0.02	0.03	0.04	0.04	0.10	0.00	0.06
Tumour size (TS)					1.00	−0.14	−0.16	0.03	0.12	0.08	0.16
ER status (ER)						1.00	0.01	0.19	−0.08	0.06	0.00
Dietary supplement (DS)							1.00	0.00	−0.02	0.04	−0.10
Psychological treatment (PT)								1.00	−0.02	0.00	−0.03
Imagery									0.31*	−0.36	−0.28
Relaxation									0.30*	−0.28	−0.26
EPQ-L									1.00	−0.14	−0.12
HADS Anxiety (Anx.)										1.00	0.45†
HADS Depression (Dep.)											1.00

HADS, Hospital Anxiety and Depression Scale; EPQ, Eysenck Personality Questionnaire. *$P<0.05$; †$P<0.01$.

Pathological responses

After completion of chemotherapy, all patients underwent surgery (except the 3 patients who died). 23 patients had breast conservation (quadrantectomy) and 70 patients had a mastectomy; all patients had axillary surgery (sample or clearance). In 62 of these patients, examination of the removed breast tissue demonstrated the presence of a residual macroscopic lesion. However, this did not necessarily contain tumour cells and in some patients comprised fibrous tissue only. Histological examination of the breast tissue using the previously defined protocol demonstrated a Type V response (complete histological response with no evidence of residual tumour) in 10 patients, Type IV in 13, Type III in 25, Type II in 25 and Type I in 20 patients.

Psychological assessments

HADS and EPQ-L scores prior to treatment are shown in Table 1. Twenty-one per cent (20/96) scored above ten on HADS anxiety, which is usually regarded as the cut-off for clinically significant anxiety. None scored above ten for HADS depression. EPQ-L scores were high in this study compared with local and national norms [22, 24, 33].

Psychological assessments and responses to chemotherapy

Intercorrelations between the ten putative prognostic variables and clinical and pathological responses are shown in Table 2.

Pathological response. Stepwise linear regression revealed that tumour size ($P=0.01$) and HADS depression ($P=0.001$) afforded the best statistical prediction (adjusted $R^2=0.17$, $F=10.47$, $P=0.0001$) (Table 3). These results were significant after adjustment for multiple correlations (multiple R^2 was 0.43 (for multiple comparisons and $\alpha=0.01$, multiple $R^2>0.17$)) [32].

Table 3. Stepwise linear regression

Variable	B	SE of B	Beta	*P*
Pathological response				
HADS depression	−0.163	0.048	−0.321	0.001
Tumour size	−1.157	0.460	−0.239	0.01
Clinical response				
HADS anxiety	0.249	0.080	0.299	0.003
Tumour size	0.616	0.283	0.210	0.03

Clinical response. Stepwise linear regression showed that tumour size ($P=0.03$) and HADS anxiety ($P=0.003$) gave the best statistical prediction (adjusted $R^2=0.12$, $F=7.77$, $P=0.0008$) (Table 3). These results were significant after adjustment for multiple correlations (multiple R^2 was 0.38 (for multiple comparisons and $\alpha=0.05$, multiple $R^2>0.17$)) [32].

DISCUSSION

As postulated, HADS depression score was a significant independent prognostic factor for pathological response to chemotherapy—the higher the score, the poorer the response. This is consistent with our previous finding that HADS depression scores predicted survival in patients with lymphoma who were treated with chemotherapy [22]. HADS anxiety score was a significant independent predictor of clinical response to chemotherapy—similarly, the higher the score the poorer the response. For clinical and pathological response, the size of the tumour at diagnosis was an independent prognostic factor of response to chemotherapy; larger tumours were likely to show a poorer response.

HADS depression scores predicted pathological response whereas HADS anxiety scores predicted clinical response only. As is usual in groups of patients unselected by the presence of concomitant psychiatric disorder, HADS anxiety and depression scores were significantly correlated in this study ($r_{xy}=0.45$, $P<0.0005$) (Table 2). If anxiety and depression scores were combined, and the multivariate analyses repeated, the combined HADS score emerged as the sole predictor of clinical response to chemotherapy. Although 21% of patients scored above ten on HADS anxiety before chemotherapy, none scored above 10 on HADS depression. Structured clinical interviews [34] before chemotherapy confirmed a low prevalence of major depression (2 cases). Depression scores in this study, therefore, were predictive of chemotherapy response at diagnostically sub-threshold values.

Although negative findings have been reported [35–37] psychological interventions have been found to affect survival in metastatic breast cancer [38, 39], malignant melanoma

[40] and lymphoma [22, 41]. However, the hypotheses that relaxation/imagery intervention and low L-scores would improve response to chemotherapy are not supported by the findings of the present study, although imagery vividness correlated with clinical response in the intervention group [25]. This may reflect differences in the biology of lymphomas and breast cancer; it remains to be seen if they will affect long-term survival. Although clinical and pathological response to chemotherapy are important factors affecting survival, the prediction is variable and other factors must be operative [42].

Dietary supplementation with L-arginine also failed to emerge as a significant independent prognostic factor, although a previous univariate analysis suggested that L-arginine potentiated the pathological response of tumours <6 cm in initial diameter [26].

In patients with metastatic colorectal cancer, Allen-Mersh and colleagues [43] found that tumour burden was positively correlated with pretreatment HADS depression scores and that these depression scores predicted survival. They postulated that a 'toxin' released by the tumour might have caused the psychological effects. In the present study with large and locally advanced breast cancer patients, tumour size was not significantly correlated with HADS anxiety and depression scores ($r_{xy} = 0.08$, $P = 0.53$; $r_{xy} = 0.16$, $P = 0.13$, respectively). This also suggests that the relationship was not due to women being more distressed because they had a larger tumour. Moreover, with respect to response to chemotherapy, anxiety and depression scores were independent predictors of response after tumour size had been taken into account.

One possibility is that anxiety and depression affected health-related behaviours. In this study, however, compliance with chemotherapy was not related to anxiety or depression. None the less, it is relevant to note that in the experimental group there were near-significant correlations between the frequency with which patients practised relaxation and HADS anxiety ($r = -0.28$, $P < 0.06$) and HADS depression $r = -0.26$, $P < 0.08$). Similarly, the self-ratings of imagery intensity were negatively correlated with anxiety ($r = -0.36$, $P = 0.01$) and depression ($r = -0.28$, $P = 0.05$).

Our findings support the postulate that psychological factors are independent predictors of tumour response to primary chemotherapy. Further work is required to confirm these results in patients with breast cancer and in other malignancies and to establish that the relationship is causal. Obvious and very significant therapeutic implications would follow the establishment of such a relationship.

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