TJC Turkish Journal of Cancer
Volume 36, No.3, 2006

Short-term health-related quality of life with epirubicin and cyclophosphamide (EC) versus 5-fluorouracil, epirubicin and cyclophosphamide (FEC) as adjuvant chemotherapy in Turkish patients with operable breast cancer

BİNNAZ DEMİRKAN[1], TUĞBA YAVUZŞEN[1], MEHMET ALAKAVUKLAR[2]

[1]Dokuz Eylül University Institute of Oncology, Department of Clinical Oncology, Division of Medical Oncology, [2]Kent Hospital, Department of Medical Oncology, İzmir-Turkey

ABSTRACT

One of the key issues during adjuvant treatments is ensuring that patients have a worthwhile health-related quality of life (HRQOL). We compared short-term HRQOL in Turkish patients with operable breast cancer receiving EC or FEC as adjuvant chemotherapy. Eligible patients (n=60) with Stage I-II and Stage III breast cancer were assigned to EC (Group I) and FEC (Group II), respectively. HRQOL was assessed with WHOQOL-BREF-TR, Beck Depression Inventory and State-Trait Anxiety Inventory at baseline and the start of cycles 2, 4 and 3 months after the last cycle. More patients with advanced stage (operable stage III) (n=26, 86.7%) and MRM (n=18, 60%) were treated with FEC ($p<0.001$ and $p= 0.07$, respectively). There were no statistically significant differences in global HRQOL between the two treatment groups. However, the comparison of the depression scores revealed an increase in Group II ($p=0.002$). Information about the expected HRQOL and psychological consequences of treatment regimens should help clinicians and their patients make informed treatment decisions.[Turk J Cancer 2006;36(3):116-125].

KEY WORDS:

Breast cancer, adjuvant chemotherapy, HRQOL, depression

INTRODUCTION

Breast cancer is the most common cancer and second leading cause of cancer death among women in developed countries (1,2). Adjuvant chemotherapy (CT) increases relapse-free survival and overall survival for women with resectable breast cancer. Polychemotherapy (combination chemotherapy) significantly decreases risk of recurrence and death from any cause compared with no polychemotherapy. The 1998 meta-analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) showed that polychemotherapy produced significant proportional annual reductions in recurrence and mortality both for women younger than age 50 (35.3% and 27.3%, $p<0.0001$) and for those aged 50 to 69 years (20.3% and 11.3%, $p<0.0001$); absolute reductions in risk ranged from 2.3% to 15.4% at 10 years depending on age and nodal status. A decade of randomized clinical trials has established the level 1 evidence-based superiority of anthracycline-based CT over CMF-like (Cyclophosphamide, Methotrexate, Fluorouracil) regimens. This superiority is smaller than expected, however, on average not exceeding a 4% absolute gain in 10-year survival for node-positive and a 1.7% gain at 5 years for node-negative breast cancer patients (3-7). In the EBCTCG Overview (September 2000), the results regarding anthracycline benefit, based on 14,000 women enrolled in 15 trials, continue to show the benefit of anthracycline regimens when compared with CMF in terms of reductions in recurrence (11% greater relative reduction, $p=0.0005$) and death (16% greater relative reduction, $p<0.00001$). The advantage of anthracycline-based CT was found almost exclusively when a three-drug regimen was used: either CEF (Cyclophosphamide, Epirubicin, Fluorouracil) or CAF (Cyclophosphamide, Adriamycin, Fluorouracil) (8-10). In the last update of the EBCTCG Overview (May 2005), it is shown that widely practicable adjuvant drug treatments also substantially reduce 15-year mortality rates (11).

Given the timing required by its use, adjuvant therapy requires the patient to absorb complex medical data and make challenging trade-offs shortly after initial diagnosis. However, many women are unprepared or unable to optimize adjuvant treatment decisions while experiencing the shock and dismay that often follow the confirmation of an invasive breast cancer diagnosis. Each woman needs to know the facts and circumstances of her own case and to fully understand the benefits and risks of adjuvant therapy. Only then can she, with her medical team, choose those therapies that will maximize her benefit as a patient and as a survivor in all aspects of her life, over both the short and longer term. So, one of the key issues in treatment of breast cancer is ensuring that patients have a worthwhile health-related quality of life. Moreover, the introduction of patients' points of view is considered a further step towards a more comprehensive humanistic approach to cancer treatment (12,13).

In recent years, more and more attention is being paid to quality of survival during and following treatment of cancers in addition to quantity of survival indices (14). Quality of Life (QOL) assessment has been used in research and clinical practice to characterize the burden created by cancer or its treatment, to select treatment options, to demonstrate the effect of rehabilitative approaches and to make policy decisions. It is generally agreed that HRQOL is a multidimensional construct that represents patient's perception of the effects of an illness and its associated therapy on his or her day-to-day functioning. While a broad range of QOL domains can be assessed, the physical, psychological, and social dimensions are the most important (15).

Until recently, research on QOL has been carried out almost exclusively among North American or Western European populations. Because socio-cultural background exerts a significant influence on the quality of a patient's life and its measure, findings from studies conducted in Western societies cannot be directly generalized cross-culturally or cross-nationally. The ways of life (i.e., the patient's family could play a different role in the management of the cancer patient), as well as the mean levels of education may be different in various countries. Moreover, different social and national health systems could cause the patient to assign a different importance to the same domains (i.e., economic conditions may be more or less important depending on whether the cost of disease is completely supported by the national health system or is totally or partially charged to the patient). Therefore, in some countries, domains different from those explored in

a questionnaire produced and validated in another country may be the most important (12,13, 16-18). This further highlights an urgent need to conduct QOL studies and generate data on the QOL of breast cancer patients in other countries such as Turkey in neoadjuvant, adjuvant, metastatic setting or follow-up period.

Our purpose was to compare short-term HRQOL in Turkish patients with operable breast cancer receiving the combination of EC or FEC as adjuvant chemotherapy.

PATIENTS AND METHODS

After the approval of local ethical committee, between July 2001 and June 2003, eligible patients (n=60) with primary operable breast cancer who were willing to participate in the study were enrolled prospectively. All patients were able to understand and give written informed consent. Stage I-II and operable Stage IIIA, IIIC cases (2002 AJCC TNM staging system) were assigned to adjuvant chemotherapy with EC (epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2, IV, on day 1 of each cycle) every three weeks for four cycles (Group I) and FEC (5-fluorouracil 600 mg/m^2, epirubicin 100 mg/m^2 plus cyclophosphamide 600 mg/m^2, IV, on day 1 of each cycle) every three weeks for six cycles (Group II) respectively. Primary surgical treatment modalities were breast conserving surgery (BCS) for stage I-II and operable Stage IIIA, IIIC except for T3 patients as well as multicentric disease that required simple mastectomy with axillary dissection (MRM). Radiation therapy was received after 4 cycles of EC regimen and 3 cycles of FEC regimen. The treatment types were classified according to the current adjuvant treatment modalities for operable breast cancer. A complete blood cell count was mandatory on days 7-10 and 20-21 of each cycle, to ascertain the neutrophil nadir count and neutrophil recovery. Other laboratory toxicities were evaluated on days 20-21 of each cycle. Clinical toxicity was carefully evaluated on day 21. Toxicity was graded using the NCI-CTC version 1.0. HRQOL was assessed by the self-administered standard Turkish version of the World Health Organization Quality of Life Instrument, Short Form (WHOQOL-BREF-TR), Beck Depression Inventory (BDI) and Spielberger's State-Trait Anxiety Index (STAI) Trait-Anxiety Scale which had been evaluated for the validity and reliability for Turkish patients, at baseline and the start of cycles 2, 4 and 3 months after the last cycle. The chosen instruments are also widely used internationally and meet the required standards for reliability and validity. Study participants proceeded with their clinical appointment as scheduled. At each appointment, they were interviewed by a physician and a psychologist. After the medical and psychological conversations, they were asked to fill in the questionnaires.

The WHOQOL-BREF is a 26-item version of WHOQOL-100 assessment. The questionnaire consists of 26 questions, scored into 4 domains: physical health (7 items), psychological well-being (6 items), social relationship (3 items) and satisfaction with the environment (8 items). It also includes one facet on overall quality of life and general health. Each item is rated on a 5-point scale and the domain scores are transformed to lie between 0 and 20 (19,20). The WHOQOL-BREF-TR is a 27-item questionnaire including one more question that reflects the patient's relationships with her close environment (i.e., husband, colleagues, relatives, friends) defining the difficulties related with the pressure and control on her.

BDI and the Spielberger's STAI-Dispositional Anxiety Subscale are self-administered 21-item and 20-item questionnaires that reflect depression and anxiety levels of the patients by their own feelings, respectively and also distinguish the other psychopathological disorders (21-25). Quantitative data were managed and analyzed with WHOQOL-BREF SPSS Syntax. The four domain scores of the BREF were calculated by summating the scores of the corresponding questions in each subscale. Pearson's correlation was used to assess the relationship between anxiety and depression scores, and the correlation between the adverse effects of chemotherapy and QOL scores or depression scores. Treatment comparisons and score change between baseline and follow-up HRQOL data were performed using statistical analysis software (SPSS 11.0 for Windows). All the scales were analyzed by using a two-sided test at the 5% significance level.

Table 1
Demographic and clinical characteristics of the study sample (n=60)

Characteristics	No. of patients (%)		P value
	EC	FEC	
Gender			
Female	30 (100%)	30 (100%)	
Age (years)			0.838
Median	47.5	49	
Range	26-63	27-67	
Stage			0.000
I	4 (13.3%)	-	
II	24 (80%)	4 (13.3%)	
III	2 (6.7%)	26 (86.7%)	
Type of operation			0.073
BCS	19 (63.3%)	12 (40%)	
MRM	11 (36.7%)	18 (60%)	
Marital Status			0.447
Unmarried	3 (10%)	4 (13.3%)	
Married	22 (73.3%)	23 (76.7%)	
Widow/Divorced	5 (16.7%)	3 (10%)	
Education			0. 309
≥ High school	18 (60%)	14 (46.7%)	
< High school	12 (40%)	16 (53.3%)	

BCS: Breast Conserving Surgery; MRM: Modified Radical Mastectomy; EC: Epirubicin, Cyclophosphamide; FEC: Fluorouracil, Epirubicin, Cyclophosphamide

Table 2
Treatment-related adverse effects (NCI-CTC version 1.0) by chemotherapy regimen (Grade 3/4)

	EC 90 (n=30)		FEC 100 (n=30)		
Adverse Effect	N	%	N	%	P value
Neutropenia	12	40.0	18	60.0	0.028
Febril Neutropenia	0	0.0	4	13.3	0.012
Thrombocytopenia	0	0.0	0	0.0	-
Anemia	2	6.6	5	16.6	0.036
Nausea/Vomiting	4	13.3	9	30.0	0.042
Stomatitis	3	10.0	6	20.0	0.048
Alopecia	24	80.0	26	86.6	0.092
Infection	0	0.0	1	3.3	0.108
Diarrhoea	0	0.0	1	3.3	0.108
Cardiotoxicity	0	0.0	0	0.0	-

Table 3
Mean scores of each domain in the Turkish version of WHOQOL-BREF

	Baseline		Cycle 2		Cycle 4		3 months after CT		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P
Physical									
EC	14.6	3.0	12.4	2.1	15.0	2.6	16.4	2.3	<0.001
FEC	15.1	3.4	12.7	1.7	14.7	3.0	16.2	2.6	<0.001
**P value	0.596		0.454		0.735		0.691		
Psychological									
EC	14.4	3.3	14.1	2.8	14.1	3.3	15.3	2.2	0.030
FEC	15.2	2.5	14.7	1.8	14.8	2.3	16.2	2.3	0.028
P value	0.275		0.325		0.344		0.098		
Social									
EC	15.8	2.7	15.0	3.0	14.4	3.0	15.3	2.3	0.038
FEC	16.6	2.5	15.7	2.4	15.0	3.5	16.4	3.3	0.026
P value	0.237		0.346		0.733		0.090		
Environment									
EC	15.4	2.3	15.4	2.3	15.5	2.3	15.8	2.1	0.369
FEC	16.1	2.0	16.1	2.0	15.8	2.1	16.3	2.0	0.391
P value	0.324		0.265		0.655		0.887		

WHOQOL-BREF: World Health Organization Quality of Life Instrument Short Form; SD: Standard Deviation; CT: Chemotherapy; EC: Epirubicin, Cyclophosphamide; FEC: Fluorouracil, Epirubicin, Cyclophosphamide
Scores range from 0 to 20, with a higher score representing a higher level of functioning
**P value of difference of mean scores over time in each treatment group*
***P value of treatment difference over time*

Table 4
Mean scores of anxiety and depression in the STAI and BDI, respectively

	Baseline		Cycle 2		Cycle 4		3 months after CT		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P
****Anxiety**									
EC	41.3	8.4	42.6	7.0	43.3	9.3	40.0	8.1	0.386
FEC	40.2	9.8	43.0	8.8	42.9	8.6	40.5	7.2	0.840
†P value	0.662		0.846		0.430		0.190		
‡Depression									
EC	9.2	5.3	9.6	5.6	11.0	7.2	7.4	4.4	0.026
FEC	9.6	4.4	11.4	6.8	10.1	4.8	11.5	5.0	0.028
P value	0.711		0.288		0.585		0.002		

STAI: Spielberger's State-Trait Anxiety Index Trait Anxiety Scale; BDI: Beck's Depression Inventory; SD: Standard Deviation; CT: Chemotherapy; EC: Epirubicin, Cyclophosphamide; FEC: Fluorouracil, Epirubicin, Cyclophosphamide
**P value of difference of mean scores over time in each treatment group*
***Scores range from 20 to 80, with a higher score representing a higher level of anxiety*
†P value of treatment difference over time
‡Scores range from 0 to 63, with a higher score representing a higher level of depression

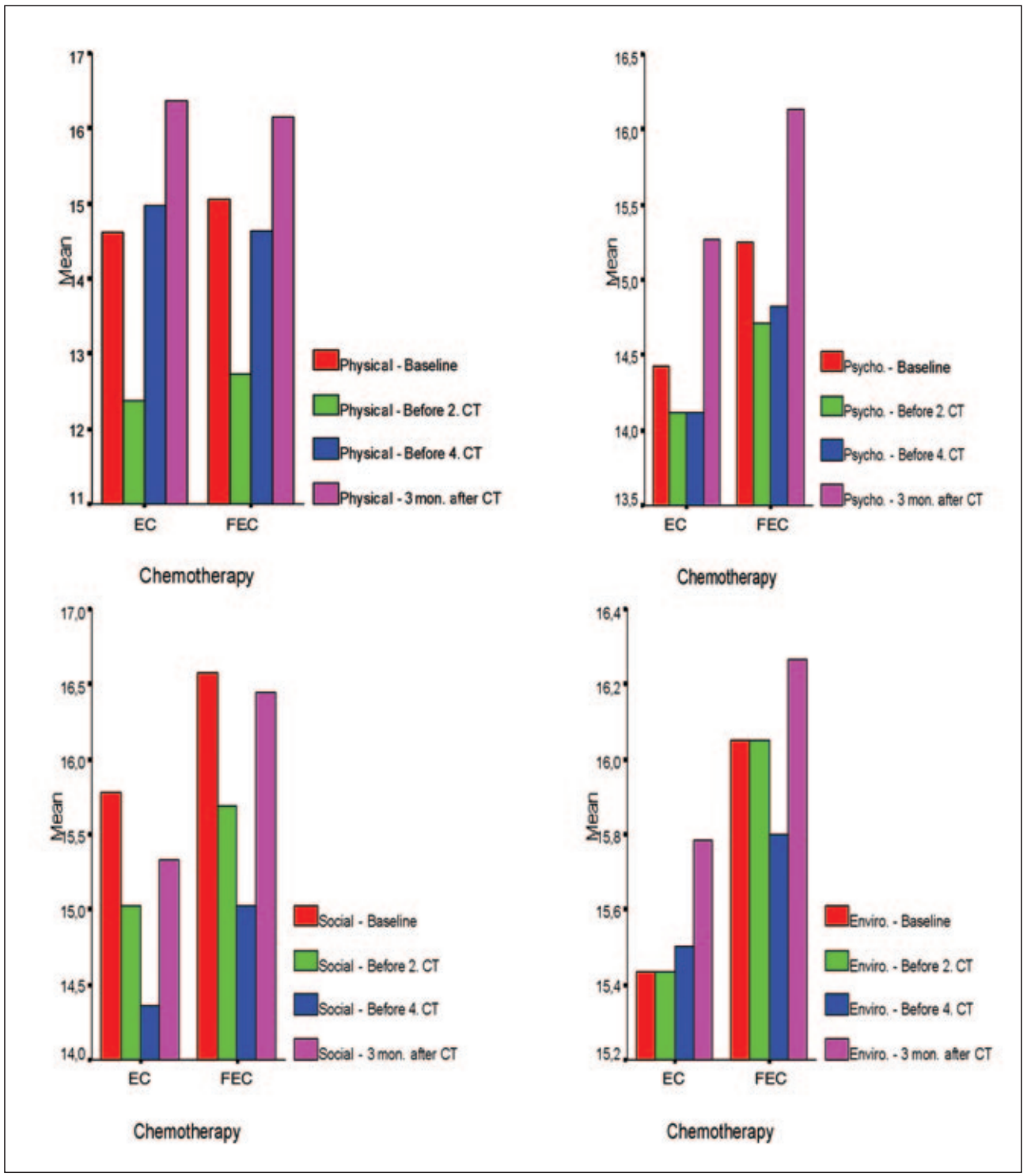

Fig 1. WHOQOL-BREF's 4 domains: physical, psychological, social and environmental according to the adjuvant treatment (EC and FEC)

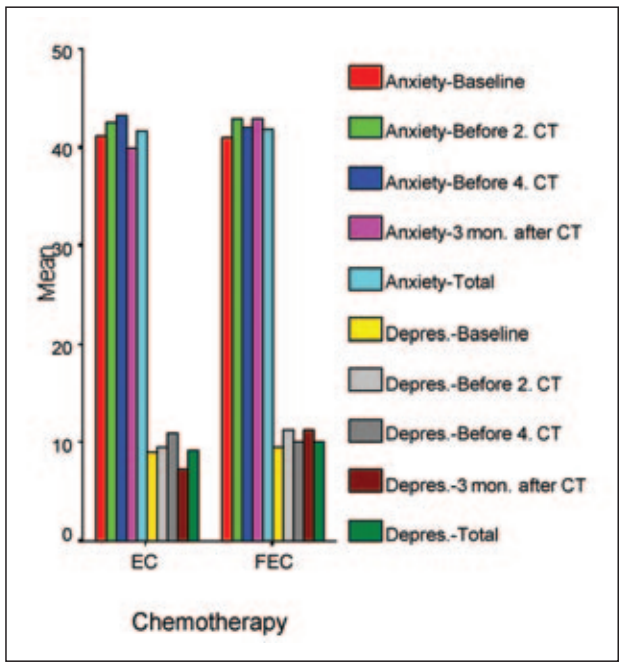

Fig 2. Anxiety and depression (STAI and BDI) according to the adjuvant treatment (EC and FEC)

RESULTS

All the patients (n=60) who accepted to take part in the study completed baseline and subsequent measures. The compliance was very well and there was no missing data because of the limited number of the study participants in a single institution. The sociodemographic characteristics of the 2 study samples are presented in table 1. More patients with operable stage III (n=27, 87%) and MRM (n=19, 63%) were treated with FEC ($p<0.001$ and $p=0.073$, respectively). The incidence of grade 3 to 4 treatment related acute toxicity is reported in table 2. Neutropenia, febrile neutropenia, anemia, stomatitis and alopecia were significantly more frequent in FEC 100 ($p<0.05$). No treatment related death was observed. We compared the WHOQOL-BREF domain scores from Group I with scores obtained from Group II. Table 3 and figure 1 show patients' mean scores for those variables that varied over time from patients with repeated questionnaires. In both groups, selected aspects of HRQOL were impaired over time significantly, with decreased physical and social/family activities and impaired psychology; however significant improvements in all these aspects were seen after the end of treatments. Table 4 and figure 2 illustrate the extent of anxiety and depressive symptoms by STAI and BDI, respectively. The anxiety scores were similar in both groups; but there were statistically significant difference between depression scores in Group I (favorable) and Group II (unfavorable) ($p=0.002$). Multiple regression analysis indicated that type of operation (MRM) and marital status (being married) were the factors affecting the depression scores ($p=0.009$ and $p=0.022$, respectively).

In the present study, age at time of diagnosis, education, type and adverse effects of chemotherapy had no impact on quality-of-life, depression and anxiety scores.

DISCUSSION

The aim of this study was the comprehensive assessment and comparison of quality of life in operable Turkish breast cancer patients receiving two different adjuvant chemotherapy regimens.

World Health Organization (WHO) defines QOL as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns " (26). An instrument based on this conceptual framework, WHOQOL-100, had been concurrently developed across several countries and cultures while retaining similar psychometric properties and structure. It is available in several culture-specific and language-specific versions. A 26-item, short form of this instrument (WHOQOL-BREF) had been developed for pragmatic reasons and has been shown to have similar psychometric properties to the WHOQOL-100 (19,20).

Today, in evaluating QOL, there is general agreement on the following points:

- we need to measure the QOL of cancer patients and its variations, possibly in relation to the clinical evolution of the disease and to treatments administered to the patients;

- a multidimensional approach should be preferred, so as to correctly interpret the observed variations of QOL, i.e. if they depend on well-being, social role, physical performance, psychological distress, etc.;

- the evaluation must be performed by the patient; no other person can have an exact perception of the patient's QOL, as it depends on his/her feeling, intelligence, philosophy of life, perceptions, and so on;

- a valid tool is mandatory: every scale must be tested for reliability and validity.

The WHOQOL-BREF is a sound, cross-culturally valid assessment of QOL, as reflected by its 4 domains: physical, psychological, social and environmental. BDI and STAI are complementary tools evaluating different aspects of psychological status of patient. All of these scales have reliable and validated Turkish versions.

The principal finding of this research is that MRM and married patients had poor quality of life due to depression. Neither type and adverse effects of chemotherapy regimen nor age and education affected quality of life and psychometric scores. Quality of life studies following breast-conserving therapy (BCT) or mastectomy has revealed that mastectomy patients had significantly lower body image, role, and sexual functioning scores and their lives were also more disrupted than BCT patients. In one study, mastectomy patients felt more self-conscious and ashamed of their body. In a more recent study, anxiety, depression, and self-esteem were also worse for mastectomy patients (27,28). So QOL was found to be useful for clinical decision-making processes during local treatment investigations. Our research did not include QOL data with a related breast module such as FACT-B or EORTC QOL-BR23 because there was no Turkish validation of them at the time of the study (29-31).

Certain limitations must be regarded in the interpretation of this study. The sample size was relatively small. Additionally, a selection bias should be recognised, as more patients with stage III and MRM were received FEC according to the nonrandomized research setting, so the results could have been misinterpreted as if the chemotherapy regimen, itself, had disrupted QOL of patients.

Most of the QOL studies have been done with breast carcinoma survivors or during primary treatment and metastatic setting until recently. To date, a few studies with adjuvant chemotherapy has been reported. Posttraumatic stress disorder, conditioned nausea, emesis, and distress as a consequence of sights, smells, and tastes triggered by reminders of their treatment, sexual problems, body image, lymphedema with/without numbness that interfere with functioning have been reported as long-term psychological and medical sequelaes (18,23, 32-35). QOL is now considered an important secondary endpoint, particularly in cancer clinical trials, together with the traditional primary clinical endpoints. In metastatic setting, HRQOL factors such as appetite loss besides known clinical factors have been found to be significant prognostic factors for survival (36-38). In conventional chemotherapy trials, global quality of life has been shown to be maintained during the treatment period, although selected aspects of HRQOL have been impaired over time. But a dose-intensive adjuvant regimen induces a higher, despite transient, psychological distress in early breast cancer patients (35, 39-41). Although research indicates a survival advantage for married persons living with a chronic disease such as cancer due to higher socioeconomic status with better access to healthcare and a protective benefit through increased social support networks, association between marital status and quality of life of cancer patients has not been thoroughly explored. In our study, not the type of chemotherapy itself but the type of operation (MRM) and the marital status (married women) were found to be the significant factors affecting depression scores and HRQOL. In recent years, body image has emerged as an important factor, with breast-conserving therapy patients being more satisfied with their appearance and having higher life-style scores. A married woman with MRM may not only feel less attractive and sexually active as a wife, but also role functioning (work, hobbies, daily habits) and contact with people may be more limited (27,28, 42-44). More researches are needed to identify the link between marital status, treatment and HRQOL of breast cancer patients. So, all these informations are important when advising women patients of the expected HRQOL consequences of treatment regimens and should help clinicians and their patients make informed treatment decisions.

In conclusion, continued monitoring and clinical interventions to address common symptoms associated with diagnosis and treatment should be considered to improve physical and emotional functioning before, during and after the primary treatment for breast cancer.

ACKNOWLEDGEMENTS

We thank Prof. Dr. Hüray Fidaner (Dokuz Eylül University School of Medicine, Department of Psychiatry), who died in August 2002, for the kind comments on the design and conduction of the study.

We would also like to acknowledge the contribution of Meliha Diriöz (Dokuz Eylül University School of Medicine, Department of Psychiatry), Ahmet Alacacıoğlu and Zuhal Başkan (Dokuz Eylül University Institute of Oncology, Department of Clinical Oncology, Division of Medical Oncology), and Yücel Demiral (Dokuz Eylül University School of Medicine, Department of Public Health) for his kind support of statistical analysis.

References

1- Coleman MP, Gatta G, Verdecchia A, et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. The EUROCARE Working Group. Ann Oncol 2003;14(suppl 5):128-49.

2- Gloeckler Ries LA, Reichman ME, Riedel Lewis D, et al. Cancer Survival and Incidence from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist 2003;8:541-52.

3- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998;352:930-42.

4- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998;351:1451-67.

5- Goldhirsch A, Wood WC, Gelber RD, et al. Meeting Highlights: Updated International Expert Consensus on the Primary Therapy of Early Breast Cancer. J Clin Oncol 2003;21:3357-65.

6- Smith IE, Jänicke F. Breaking barriers: Recent advances in the treatment of breast cancer. The Breast 2004;13(Suppl 1):S1-S38.

7- Cardoso F, Piccart MJ. The best use of chemotherapy in the adjuvant setting. Breast 2003;12:522-8.

8- Coates A, Goldhirsch A, Gelber R; International Breast Cancer Study Group. Overhauling the breast cancer overview: are subsets subversive? Lancet Oncol 2002;3:525-6.

9- Cardoso F, Atalay G, Piccart MJ. Optimising anthracycline therapy for node positive breast cancer. Am J Cancer 2002;1:257-68.

10- Piccart MJ, Cardoso F, Di Leo A, et al. Areas of controversy in the adjuvant systemic therapy of endocrine-nonresponsive breast cancer. In: Perry MC, editor. American Society of Clinical Oncology (ASCO) Educational Book, Spring. Alexandria, VA: ASCO, 2002;144-155.

11- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.

12- Roila F, Cortesi E. Quality of life as a primary end point in oncology. Ann Oncol 2001;12(Suppl 3):S3-S6.

13- Mosconi P, Colozza M, De Laurentiis M, et al. Survival, quality of life and breast cancer. Ann Oncol 2001;12(Suppl 3):S15-S19.

14- Pandey M, Singh SP, Behere PB, et al. Quality of life in patients with early and advanced carcinoma of the breast. Eur J Surg Oncol 2000;26:20-4.

15- Albert US, Koller M, Lorenz W, et al. Quality of life profile: from measurement to clinical application. The Breast 2002;11:324-34.

16- Tamburini M. Health related quality life measures in cancer. Ann Oncol 2001;12(Suppl 3): S7-S10.

17- Chie WC, Chang KJ, Huang CS, et al. Quality of life of breast cancer patients in Taiwan: Validation of the Taiwan Chinese version of the EORTC QLQ-C30 and EORTC QLQ-BR23. Psychooncology 2003;12:729-35.

18- Cui Y, Shu X, Gao Y, et al. The long-term impact of medical and socio-demographic factors on the quality of life of breast cancer survivors among Chinese women. Breast Cancer Res Treat 2004;87:135-47.

19- Saxena S, Carlson D, Billington R; WHOQOL Group. World Health Organisation Quality Of Life. The WHO quality of life assessment instrument (WHOQOL-BREF): the importance of its items for cross-cultural research. Qual Life Res 2001;10:711-21.

20- Skevington SM, Lotfy M, O'Connell KA; WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL Group. Qual Life Res 2004;13:299-310.

21. Beck AT. Measuring depression: The Depression Inventory. In: Williams TA, Katz MM and Shield JA, editors. Recent advances in the psycho-biology of the depressive illnesses. Washington: Government Printing Office, 1972;299-301.

22. Spielberger CD, Gorsuch RL, Lushene RE. Manual for State-Trait Anxiety Inventory. California: Consulting Psychologists Press, 1970.

23- Pemberger S, Jagsch R, Frey E, et al. Quality of life in long-term childhood cancer survivors and the relation of late effects and subjective well-being. Support Care Cancer 2005;13:49-56.

24- Morasso G, Costantini M, Baracco G, et al. Assessing psychological distress in cancer patients: validation of a self administered questionnaire. Oncology 1996;53:295-302.

25. Allen R, Newman SP, Souhami RL. Anxiety and depression in adolescent cancer: Findings in patients and parents at the time of diagnosis. Eur J Cancer 1997;33:1250-5.

26- van der Steeg AFW, De Vries J, Roukema JA. Quality of life and health status in breast carcinoma. Eur J Surg Oncol 2004;30:1051-7.

27- Engel J, Kerr J, Schlesinger-Raab A, et al. Quality of life following breast-conserving therapy or mastectomy: Results of a 5-year prospective study. The Breast Journal 2004;10:223-31.

28- Nissen MJ, Swenson KK, Ritz LJ, et al. Quality of life after breast carcinoma surgery: a comparison of three surgical procedures. Cancer 2001;91:1238-46.

29- Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. JNCI 1993;85:365-76.

30- Sprangers MAG, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer- Specific Quality-of-Life Questionnaire Module: First results from a Three-Country Field Study. J Clin Oncol 1996;14:2756-68.

31- Nagel GC, Schmidt S, Strauss BM, et al. Quality of life in breast cancer patients: a cluster analytic approach. Breast Cancer Res Treat 2001;68:75-87.

32- Ahles TA, Saykin AJ, Furstenberg CT, et al. Quality of life of long-term survivors of breast cancer and lymphoma treated with standard-dose chemotherapy or local therapy. J Clin Oncol 2005;23:4399-406.

33- Broeckel JA, Jacobsen PB, Balducci L, et al. Quality of life after adjuvant chemotherapy for breast cancer. Breast Cancer Res Treat 2000;62:141-50.

34- de Haes H, Olschewski M, Kaufmann M, et al. Quality of life in Goserelin-treated versus Cyclophosphamide + Methotrexate + Fluorouracil – treated premenopausal and perimenopausal patients with node-positive, early breast cancer: The Zoladex Early Breast Cancer Research Association Trialists Group. J Clin Oncol 2003;21:4510-6.

35- Del Mastro L, Costantini M, Morasso G, et al. Impact of two different dose-intensity chemotherapy regimens on psychological distress in early breast cancer patients. Eur J Cancer 2002;38:359-66.

36- Efficace F, Therasse P, Piccart MJ, et al. Health related quality of life parameters as prognostic factors in a nonmetastatic breast cancer population: An international multicenter study. J Clin Oncol 2004;22:3381-8.

37- Coates AS, Hürny C, Peterson HF, et al. Quality-of-life scores predict outcome in metastatic but not early breast cancer. J Clin Oncol 2000;18:3768-74.

38- Efficace F, Biganzoli L, Piccart M, et al. Baseline health-related quality-of-life data as prognostic factors in a phase III multicentre study of women with metastatic breast cancer. Eur J Cancer 2004;40:1021-30.

39- Bottomley A, Biganzoli L, Cufer T, et al. Randomized, controlled trial investigating short-term health-related quality of life with doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first line chemotherapy in patients with metastatic breast cancer: EORTC Breast Cancer Group, Investigational Drug Branch for Breast Cancer and the New Drug Development Group Study. J Clin Oncol 2004;22:2576-86.

40- Morgan G, Ward R, Barton M. The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies. Clinical Oncology 2004;16:549-60.

41- Land SR, Kopec JA, Yothers G, et al. Health related quality of life in axillary node-negative, estrogen receptor-negative breast cancer patients undergoing AC versus CMF chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel Project B-23. Breast Cancer Res Treat 2004;86:153-64.

42- Goodwin JS, Hunt WC, Key CR, et al. The effect of marital status on stage, treatment and survival of cancer patients. JAMA 1987;258: 3125-30.

43- Kravdal O. The impact of marital status on cancer survival. Soc Sci Med 2001;52:357-68.

44- Osborne C, Ostir GV, Du X, et al. The influence of marital status on the stage at diagnosis, treatment and survival of older women with breast cancer. Breast Cancer Res Treat 2005;93:41-7.