Quality of Life in Breast Cancer Patients using Neoadjuvant AC (Doxorubicin and Cyclophosphamide) in Comparison with PG (Paclitaxel and Gemcitabine) Therapy

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Abstract

Background: Quality of life has become a part of the evaluation criteria for cancer therapy. The aim of this study was to evaluate the quality of life in breast cancer patients under chemotherapy regimens that contained doxorubicin and cyclophosphamide (AC) compared to paclitaxel and gemcitabine (PG).

Methods: This cohort study evaluated 100 women with breast cancer treated by doxorubicin and cyclophosphamide or gemcitabine and paclitaxel regimens. We used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 to assess health related quality of life at the beginning and end of chemotherapy. Data were analyzed by the independent t-test at a significance level of 0.05.

Results: Most of the 100 patients were married (68%), aged 41-50 years (36%), non-college educated (76%), and had insurance (97%). The mean quality of life scores at the first session of chemotherapy and prior to the onset of treatment-related adverse events were 71.33 for the doxorubicin and cyclophosphamide groups and 71.15 for the gemcitabine and paclitaxel groups. Analysis of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 at the last chemotherapy session showed that the quality of life in both groups deteriorated as a result of side effects. The mean of quality of life scores at the first session of chemotherapy were 66.49 for the doxorubicin and cyclophosphamide group and 59.99 for the gemcitabine and paclitaxel group.

Conclusion: Strategies to improve the emotional and role functions of the patients who undergo treatment should be given priority. Financial difficulties faced by breast cancer patients should be addressed from a policy making level at the initiating health financing system.

Keywords: Quality of life, Breast cancer, Neoadjuvant therapy, Doxorubicin and cyclophosphamide, Gemcitabine and paclitaxel

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MEJC
Middle East Journal of Cancer

Introduction

Cancer is the second most common cause of death in developed countries after cardiovascular disease and the third most common reason for mortality in developing countries, with an estimated 7.6 million deaths worldwide in 2008.[1,2] Breast cancer is the most common type of tumor and the leading cause of cancer deaths in women. It accounts for 23% (1,380,000) of all new cancer cases and 14% (458,400) of all cancer deaths.[2] In Iran, breast cancer is the most common cancer in women, and accounts for 21.4% of all cancers among females.[3] An increased trend for breast cancer mortality in Iran from 1.40 to 3.52 per 100,000 (1995 to 2004) has been reported.[4] Breast cancer affects Iranian women at least one decade earlier than their counterparts in developed countries.[5] The majority of cases in developed countries are detected and cured at stage I. In Iran, many cases are detected in the second or third stages.[6] There are several therapeutic approaches to treat these patients. Each has its own particular effects and complications which can determine a patient's survival and quality of life (QOL).[7] Due to the lack of a comprehensive reference protocol for the use of neoadjuvant therapy, various therapeutic regimens have been implemented in the treatment of breast cancer.[8] Traditionally, neoadjuvant chemotherapy, also known as primary or preoperative chemotherapy, has been used to treat women with locally advanced breast cancer in an attempt to render the tumor operable.[9,10] Anthracycline and taxane-based regimens are the backbones of most neoadjuvant chemotherapy protocols for breast cancer.[11] The AC regimen of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles has been a standard chemotherapy option since 1975.[12] The incorporation of anthracyclines further improves response rates and time to progression beyond those obtained with combinations that consist of medications other than anthracyclines.[13,14] Alternatively, the PG regimen that consists of paclitaxel 175 mg/m^2 and gemcitabine 1000 mg/m^2 every 3 weeks for 4 cycles, as a neoadjuvant regimen, is used in an attempt to obtain a better response.[15] Diagnosis of breast cancer is a tragic event for a woman. Caring for breast cancer patients can increase the risk for depression, anxiety, insomnia, and diminish QOL.[16] Health-related QOL (HRQOL), or QOL, indicates a subjective and multidimensional concept commonly composed of physical, social, emotional, mental, and functional health domains.[17] In other words, QOL characterizes the conditions of physical, psychological, and social well-being.[18] Due to the lack of studies on this topic, this study aims to evaluate QOL in Iranian breast cancer patients under treatment with the AC compared to the PG chemotherapy regimens.

Materials and Methods

This was a cohort study conducted on 100 women diagnosed with breast cancer who attended Nemazee Hospital, a referral center in Shiraz, Southern Iran during March 2013 to March 2014. We randomly assigned 100 patients with pathological diagnoses of breast cancer to 2 categories. Group 1 received PG [paclitaxel (175 mg/m^2) and gemcitabine (1000 mg/m^2)] on days 1 and 8. Both regimens were repeated every 3 weeks for a total of 4 cycles of chemotherapy. All patients had locally advanced breast cancer (stages IIB or III). All women with pathologically proven breast cancer; younger than 65 years of age; advanced breast cancer diagnosis; and Karnofsky performance status ≥70 were eligible to enter the study. In addition, all patients had normal renal and hepatic functions, Hb>9, platelets >100000, and a neutrophil count >1500. The exclusion criteria were: age more than 75 years; hypersensitivity to the chemotherapeutic agents; distant metastasis; history of chemotherapy; and abnormalities in blood tests prior to onset of chemotherapy. The present study was approved by the Ethics Committee of Shiraz University of Medical Sciences. The aim of the research and interview method was explained to the participants. All patients signed an informed consent. Patients who refused to enter the study were also excluded.

Table 1. Frequency according to the demographic characteristics of breast cancer patients.

Variable		AC (n=50)	PG (n=50)	Patients N (%)
Age (years)	≤40	11	14	25 (25)
	41-50	18	18	36 (36)
	51-60	12	11	23 (23)
	61-70	9	7	16 (16)
Marital Status	Married	36	32	68 (68)
	Single	14	18	32 (32)
Education	College education	10	14	24 (24)
	Non-college education	40	36	76 (76)
Insurance	Yes	50	47	97 (97)
	No	0	3	3 (3

AC: Doxorubicin and cyclophosphamide; PG: Paclitaxel and gemcitabine.

We used the European Organization for Research and Treatment of Cancer QOL Questionnaire-Core30 (QLQ-C30) to assessment QOL in these patients.[19] This questionnaire is a valid, reliable questionnaire to evaluate QOL in Iran.[20,21] The EORTC QLQ-C30 is a 30-item questionnaire composed of multi-item scales and single items that reflect the multidimensionality of the QOL construct. It incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea and vomiting), and a global health and QOL scale. Also six single items assess additional symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial impact of the disease and treatment). The scores are transformed into 0-100 point scales. In the questionnaire, the highest score in performance scale represents a better level of functioning. The highest score in the overall health-status scale represents a better level of QOL. However, in the symptom scale, high scores represent a worse level of symptoms.[22] The data have been collected by patient interviews during the first and last chemotherapy sessions. At the beginning of each interview, we explained the overall goal of the project and the interview was explained to each patient separately. In order to compare the mean score of the two groups in each interview, an independent t-test was used after being assured of the normality of the data. *P*-values less than 0.05 were considered statistically significant.

Results

A total of 100 patients with locally advanced breast cancer (stages IIB or III) participated in this study. There were 50 women (50%) who received the AC chemotherapy regimen and 50 women (50%) who received the PG chemotherapy regimen. Patients were between the ages of 28-70 years. In the AC regimen, the age range was 32-70 years and for the PG regimen, patients were 28-68 years of age. The majority were married (68%), 41-50 years of age (36%), not college educated (76%), and had insurance (97%). Table 1 shows the patients' demographic characteristics.

Table 2 shows a comparison of the mean QOL scores at the first session of chemotherapy and before revealing the therapeutic side effects. There were no significant differences between the study arms in different components of the questionnaire.

Analysis of the EORTC-QLQ-C30 questionnaire at the last session of chemotherapy showed that the QOL in both groups deteriorated as a result of side effects.

Table 3 compares the mean QOL scores at the end of chemotherapy and after revealing the therapy side effects. The function scales showed that the AC arm had a significantly higher mean score for the role, social, and cognitive functioning compared to the PG arm. The PG arm had a higher mean score for emotional functioning compared to the AC arm. There was no statistically significant difference in physical performance between both treatment arms.

The results of the symptoms scale of the EORTC-QLQ-C30 questionnaire showed that

Table 2. Quality of life (QOL) in AC and PG groups at the first chemotherapy session.

	AC		PG		P-value
	Mean	SD	Mean	SD	
Functional status*					
Physical	77.86	14.47	77.32	16.60	0.886
Role	67.99	18.69	67.32	15.77	0.758
Emotional	63.33	13.46	63.16	20.62	0.260
Cognitive	82.33	16.29	81.66	17.89	0.962
Social	82.66	15.41	82.33	18.26	0.820
Global health status/QOL	71.33	19.71	71.15	19.14	0.808
Symptoms**					
Fatigue	24.44	15.55	24.88	16.73	0.891
Nausea and vomiting	4.99	9.66	4.33	11.06	0.315
Pain	25.33	21.62	25.66	21.08	0.751
Dyspnea	1.99	7.25	1.99	7.99	0.732
Insomnia	23.99	25.23	23.99	25.23	1.000
Appetite loss	31.99	25.15	31.99	26.04	0.994
Constipation	17.46	21.45	17.99	23.52	0.904
Diarrhea	0.66	4.71	0.66	4.71	1.000
Financial difficulties	35.99	26.79	35.99	19.57	0.965

*A high score represents a better level of functioning.; **A high score represents a worse level of symptoms.; AC: Doxorubicin and cyclophosphamide; PG: Paclitaxel and gemcitabine.

fatigue, pain, constipation, and economic status in the AC arm were significantly better (lower mean scores) compared to the PG arm. Nausea and vomiting, dyspnea, insomnia, and diarrhea in the PG arm were better (lower mean scores) compared to PG arm.

A comparison of loss of appetite in both groups showed no significant difference. Analysis of global health status of the EORTC-QLQ-C30 questionnaire in the last session of chemotherapy in both arms showed no significant difference.

Discussion

The QOL EORTC-QLQ-C30 is part of the evaluation criteria for cancer therapy. Recently, it has been recognized that a more comprehensive assessment of the cancer patient is necessary and the evaluation of outcomes must move beyond traditional biomedical endpoints to include assessments of the impact of disease and its treatment on patient QOL.[19] This study has focused on women with stage IIB or III breast cancer. Although not the most advanced stage of disease, women with stage IIB or III breast cancer experience tremendous distress due to their diagnosis, treatment, and the fear of breast cancer recurrence or metastases. In this follow-up study,

we have presented the results of a comprehensive assessment of QOL in these patients treated with the AC chemotherapy regimen compared to the PG regimen. This study has shown that at the end of chemotherapy, QOL in both groups deteriorated as a result of the side effects and reveals the difference from the initial results. The toxicity of chemotherapy drugs causes side effects that include bone marrow suppression, immune system suppression, liver toxicity, skin disorders, central nervous system disorders, and genitourinary and gastrointestinal complications such as inflammation of the lining of the mouth and intestines.[23] Hürny et al. have reported a significant relationship between chemotherapy and the QOL of women with breast cancer.[24] Stein et al. showed that women with breast cancer treated with radiotherapy and chemotherapy suffered from poor sleep quality and had lower QOL.[25] Hatam et al. observed a vast increase in side effects such as constipation, nausea, stomatitis, fatigue, and alopecia during chemotherapy.[7] The results of the EORTC-QLQ-C30 questionnaire at the last session of chemotherapy in the current study showed that the greatest problem in the functional scales for patients who received the AC chemotherapy

Table 3. Quality of life (QOL) in AC and PG groups at the last chemotherapy session.

	AC		PG		*P*-value
	Mean	**SD**	**Mean**	**SD**	
Functional status*					
Physical	73.72	18.38	70.79	17.13	0.355
Role	68.32	17.25	58.66	12.25	0.000
Emotional	58.99	12.46	66.33	12.01	0.014
Cognitive	79.66	16.93	70.32	13.58	0.008
Social	79.32	16.68	68.99	15.43	0.016
Global health status/QOL	66.49	18.09	59.99	18.59	0.051
Symptoms**					
Fatigue	31.10	8.39	44.88	19.04	0.000
Nausea and vomiting	38.66	16.64	25.99	19.38	0.003
Pain	28.99	19.86	39.32	15.34	0.006
Dyspnea	33.33	27.76	3.33	10.10	0.000
Insomnia	46.66	33.67	27.33	25.80	0.004
Appetite loss	35.99	29.22	41.32	27.40	0.246
Constipation	19.33	27.83	50.06	22.44	0.000
Diarrhea	7.33	13.94	1.99	7.99	0.022
Financial difficulties	54.66	27.56	66.86	26.46	0.031

*A high score represents a better level of functioning; **A high score represents a worse level of symptoms.; AC: Doxorubicin and cyclophosphamide; PG: Paclitaxel and gemcitabine.

regimen was related to emotional function; patients who received PG chemotherapy had a greater problem with role function. Previous studies indicated that breast cancer had the greatest effect on role and emotional functions.[26,27] This finding was similar to the current study outcomes. Analysis of the EORTC-QLQ-C30 questionnaire in the symptom scales showed that financial difficulties received the highest rating in both arms; a higher score in this scale represented a worse situation. Mohadesi et al., in a review on QOL in patients with breast cancer, concluded that the economic situation was the most important concern that affected patients' QOL.[27] In this study, the most common complication caused by treatment in patients who received the AC chemotherapy regimen was insomnia. Insomnia is a sleep disorder characterized by trouble falling sleep, staying asleep, or waking up too early.[28] It has been shown that insomnia is a common problem in cancer patients which may occur with greater frequency and/or severity in breast cancer compared to other cancers.[29-31] There is no information on the impact of AC chemotherapeutic agents on insomnia. A systematic review has concluded that women with breast cancer tended to report higher levels of sleep disturbances upon receiving chemotherapy or radiotherapy.[32] George et al. reported an association between radiotherapy and chemotherapy with insomnia in different types of cancers.[33] Hatam et al.[7] researched QOL and toxicity in breast cancer patients who received adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) compared doxorubicin, cyclophosphamide, and 5-fluorouracil (FAC). They concluded that insomnia was the most common complication in both groups. We have observed that constipation was the most common complication in the PG arm. Although constipation is a significant side-effect of cancer treatment,[34-37] scant research has been conducted into the underlying mechanisms. Chemotherapy-induced constipation is recognized as a mixture of reduced frequency of bowel action and increased stool consistency.[38] Increasing age and female gender are thought to be associated with an increased prevalence of constipation.[39] Patients who received PG chemotherapy had a significantly higher mean score for fatigue compared to patients who received the AC chemotherapy regimen. Higher average scores in this scale have represented a worse situation.

Fatigue has a profoundly negative impact on QOL in patients with cancer by creating a tremendous interaction with patient function. Fatigue is a common symptom experienced by cancer patients[40,41] with a reported prevalence of 60%-100%, considering the cancer type, stage, and prescribed treatment.[42] Mohadesi et al. have concluded that fatigue was the most common complication caused by treatment in patients with breast cancer.[27] The findings also showed that, in addition to fatigue, patients in the AC arm had significantly better scores (lower mean scores) for pain, constipation, and economic status compared to the PG arm. The symptoms of nausea and vomiting, dyspnea, insomnia, and diarrhea in the PG arm compared to the AC was better (lower mean scores). A comparison of loss of appetite in both groups showed no significant difference. Analysis of the global health status in the last session of chemotherapy showed no significant difference between the AC and PG groups.

Acknowledgments

Conflict of Interest

No conflict of interest is declared.

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