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Quality of life and toxicity in breast cancer patients using adjuvant TAC (docetaxel, doxorubicin, cyclophosphamide), in comparison with FAC (doxorubicin, cyclophosphamide, 5-fluorouracil)

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Abstract
Objectives The aim of this study was to compare two regimens of chemotherapy in patients with breast cancer, including FAC (doxorubicin, cyclophosphamide, and 5-fluorouracil) and TAC (docetaxel, doxorubicin and cyclophosphamide); and analyze the toxicity of these treatments and observe patient's health-related quality of life.
Methods Health-related quality of life was assessed for up to 4 months (from the beginning to the end of chemotherapy cycles), using European organization and cancer treatment quality of life questionnaire (EORTC) QLQ-C30. A group of 100 patients, with node-positive breast cancer were studied in order to compare the toxicity of adjuvant therapy TAC with FAC and the subsequent effects on the patient's quality of life.
Results After a 4-month follow-up of patients, our findings showed that despite having the same mean score of QOL at the start of adjuvant chemotherapy, the QOL in TAC arm was decreased more as a result of the higher range of toxicity in TAC regimen.
Conclusion In spite of increase in disease-free patients who received TAC regimen and increase their survival rate, there is significant toxicity and decrease in QOL in TAC protocol compare to FAC protocol. Using prophylactic granulocyte colony stimulating factor (G-CSF) along with increased education aimed at improving patient's knowledge and also the provision of a supportive group involving psychiatrics and patients that have successfully experienced the same treatment may be helpful.

Keywords Quality of life · Toxicity · Adjuvant therapy · Breast cancer

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Introduction

Cancer is one of the main underlying factors for many medical disorders, disabilities and also increases mortality rate. The number of cases is increasing every day and is a worldwide concern [1]. In Iran, cancer has been rated as the third cause of mortality following coronary heart disease and road-related accidents. More than 30,000 Iranians die because of cancer annually. Furthermore, it is expected that every year there is more than 70,000 new cases and that within the next two decades the figures will double. Most of this high increase is expected due to increment of life expectancy [2].

Breast cancer is the most common malignancy amongst women in both developed and developing countries [3]. Breast cancer amounts to 32% of all cancers in women and is the cause of 19% of cancer related deaths [4].

There are several therapeutic approaches to help in the treatment of these patients. Each has its own particular effects and complications which can determine a patient's

survival and QOL. These approaches are divided into three major branches: surgery, radiotherapy and drug therapy. The later involving chemotherapy, biologic and hormone therapy. It should be noted that patients who only undertake surgery may decrease their chance of survival [5]. In order to control and recover from the disease and increase their chance of survival, adjuvant therapy is used to destroy or decrease the possibility of making small metastasis. The survival rate after completing the therapy ranges from 50 to 90%. Both the clinical treatment and the patient's own individual pathological response have a significant effect on the success of the treatment.

Certain factors such as the tumor size, tumor condition, estrogen receptors and the presence or absence of metastasis are just some of the contributing factors that have an effect on the patient's responses. Additionally, factors such as the emotional and psychological state of the patient can be an important determinant in the responses to the therapy. It is a fact that adjuvant therapy does entail significant physical and mental complications which may cause a lack of acceptance on the patient's side [6].

Due to the lack of a comprehensive reference protocol for the use of adjuvant therapy [7], various therapeutic regimens have been implemented in the treatment of breast cancer. One of the more recent methods is the utilization of docetaxel in TAC regimen containing doxorubicin and cyclophosphamide more than docetaxel. Another worldwide accepted chemotherapy protocol is FAC which is a combination of doxorubicin, cyclophosphamide and 5-fluorouracil.

Using TAC regimen is associated with a higher rate of disease-free periods and an in general survival rate at 5 years. These are significant when compared with other anthracycline-based regimens such as FAC. This is in spite of the fact that TAC has been recognized as having a significantly greater toxicity than FAC. Today, in comparison to FAC, TAC is widely used as an adjuvant therapy.

In this study, toxicity and side effects of TAC compared with FAC have been investigated. Each type of combination chemotherapies affects different domains and aspects of health-related quality of life [8, 9], that can be due to therapy side effects and other mental, social economical factors. In this study the health-related quality of life in patients with both of TAC or FAC regimen at the first and last session of chemotherapy was surveyed as well.

Materials and methods

This is a cohort double-blind study of 100 women suffering from breast cancer who had started appropriate adjuvant therapy after breast surgery who were selected by goal-oriented sampling from September 2008 to September 2009 in Shiraz, Iran, which is a referral center for about one-quarter of Iranian population. Inclusion criteria were all women with pathological proven breast cancer with involvement of auxiliary lymph nodes that were younger than 75 years old. Tolerance of chemotherapy for 6 cycles; patients with severe renal, hepatic impairment; Karnofsky performance status less than 70; age more than 75 years; hypersensitivity to the chemotherapeutic agents; patients with distant metastasis and node-negative cases were excluded. Patients' characteristics are shown in Table 1. The patients were divided in two groups after a physician had chosen their types of regimen. Thirty-two women received TAC via an IV route in the First day of chemotherapy as docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 every 3 weeks for six cycles and 68 received FAC via IV route in the first day of chemotherapy as: 5-fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2. They received this treatment every 3 weeks, for six cycles.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (EORTC QLQ-C30) was used. Reliability and validity of the questionnaire in the native language of 12 ethnic-cultural groups was recognized by Spain and the USA [10]. In addition, it was distinguished as an appropriate tool for measuring the quality of life in breast cancer by Montazeri et al. [11] and Haji Mohammadi et al. [12] in another study confirmed its validity and reliability in Iran.

This questionnaire consisted of five scales (physical, role, emotional, cognitive and social), six single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties), three symptom scales (fatigue, nausea and vomiting, pain) and an overall health-status scale. In the questionnaire, raw scores are considered from 0 to 100 and the highest score represents a high level of functioning or HRQOL, excluding single-item scales in which high scores represent a high level of symptoms.

In order to compare the quality of life in the two groups, after taking an informed consent from all the participants,

Table 1 Chemotherapy regimens by age

Regimen	TAC		FAC		Total	
	n	%	*n*	%	*n*	%
Age						
30–39	6	18.75	19	27.94	25	25
40–49	15	46.87	24	35.29	39	39
50–59	8	25	13	19.12	21	21
60–69	3	9.37	10	14.7	13	13
70 and more	–	–	2	2.94	2	2
Total	32	100	68	100	100	100

the questionnaire was used during the interview at the first session of chemotherapy and after 4 months of follow-up, at the last session (6th) of chemotherapy for each participant (they were interviewed on the bed while taking chemotherapy). Meanwhile, all the side effects and toxicity items were gathered by a well-designed checklist for both groups at the sixth session of the adjuvant therapy.

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* value less than 0.05 was considered as statistically significant.

Results

This study was performed on 100 patients suffering from breast cancer, 68 (68%) of whom were treated by FAC and 32 patients (32%) with TAC. The average mean of their age ranged 48.49 ± 10.63 (the youngest age was 30 and the oldest was 74). When separating the patients in each group, there was a mean of 49.29 ± 11.59 the least age was 30 and the highest was 74 in the FAC arm and in the TAC group, the least age was 34 and the most was 67 with a mean of 46.71 ± 8.23 (Table 1). The results showed that a large percentage of the patients were illiterate or had only an elementary education meaning that 70% (70 patients) did not have a school and only 10% (10 patients) were university graduates.

The results showed significant difference between the stages of the cancer in the stage of IIIB and IIIC and the average mean of quality of life score. Furthermore, there was a significant differences between estrogen and progesterone receptors in both positive and negative status and pre/post menopause and HER2 (negative and positive) with the score of QOL in two group of TAC and FAC. Histology data showed only significant difference between infiltrating ductal carcinoma and the score of QOL in FAC arm, but no significant difference between another histological data. In surgery part, there was significant difference between mastectomy and QOL in FAC arm and conservative surgery and QOL in TAC arm (Table 2).

Table 2 Patient characteristics in FAC and TAC regimen with: health-related quality of life

Patient characteristics	TAC ($n = 32$)	FAC ($n = 68$)	*P* value
Stage of patient			
IIA	3	9	0.05
IIB	4	8	0.06
IIIA	16	35	0.05
IIIB	3	2	0.02
IIIC	2	14	0.011
Estrogen and progesterone receptor (ER and/or PR)			
ER and/or PR positive	21	42	0.01
ER-PR negative	11	26	0.02
Premenopause	***19***	42	0.03
Postmenopause	***13***	26	0.01
HER2/neu positive	21	30	0.02
HER2/neu negative	11	38	0.03
Histology			
Infiltrating ductal carcinoma	28	57	<0.005
Modularly carcinoma	4	9	0.05
Lobular	0	2	0.08
Surgery			
Mastectomy	5	57	<0.005
Conservative surgery	27	11	<0.005

It should be noticed that the mean score of QOL in the FAC group was 68 (67.74 ± 26.11) and in the TAC group was reported 64 (64.39 ± 29.56) out of 100 and the relationship between the items stated in this table are quoted in comparison with patients quality of life. $P < 0.05$ was considered as statistically significant

Health-related QOL

Table 3 shows that the health-related quality of life after the first session of chemotherapy and before revealing the side effects of the therapy, did not have any significant differences in either of the function status and that the symptoms experienced from TAC or FAC, and the mean score of quality of life in both groups were the same.

Table 4 shows that at the final (6th) session of chemotherapy, the quality of life in both groups had deteriorated as a result of side effects and the reveals the difference from initial results. However, the decrease was higher in the TAC arm, resulting in a mean score of QOL in the FAC which group reduced from 74.5 to 68 (67.74 ± 26.11) and the TAC group decreased from 74.5 to 64 (64.39 ± 29.56).

In all the five aspects of patient's functional status (physical, role, emotional, cognitive and social functioning) and global health status/QOL, in the TAC group, the mean results were significantly less than that of the FAC group (Table 4).

Toxicity

Regarding the symptoms, the patients in the TAC arm experienced significantly worse condition (higher mean) than those patients in FAC group. These symptoms included fatigue, pain, insomnia and diarrhea. There were also other obvious differences between the two groups with regards to dyspnea, loss of appetite and constipation. Other symptoms such as nausea and vomiting were significantly less in the TAC group than in the FAC group. It was also discovered that patients experienced financial difficulties

Table 3 QOL in TAC and FAC at the first session of chemotherapy

	FAC		TAC		*P* value
	Mean	SD	Mean	SD	
Function status[a]					
Physical	64.20	23.85	64.12	24.14	0.59
Role	69.29	33.26	69.35	32.11	0.53
Emotional	62.70	34.11	62.29	30.17	0.58
Cognitive	75.12	26.21	75.13	27.19	0.59
Social	73.10	28.11	73.14	28.56	0.61
Global health status/QOL	69.39	35.14	69.33	34.82	0.59
Symptoms[b]					
Fatigue	35.13	20.89	35.11	21.14	0.62
Nausea and vomiting	2.70	11.10	2.19	11.39	0.72
Pain	27.18	25.78	27.14	25.19	0.58
Dyspnea	8.19	14.99	8.10	15.33	0.55
Insomnia	38.80	25.11	38.80	25.17	0.59
Appetite loss	18.32	31.31	18.35	32.18	0.60
Constipation	9.15	21.18	9.13	21.82	0.58
Diarrhea	1.57	10.21	1.50	10.98	0.69
Financial difficulties	38.93	33.14	35.91	39.13	0.71

[a] A high score represents a better level of functioning

[b] A high score represents a worse level of symptoms

Table 4 QOL in TAC and FAC at the sixth session of chemotherapy

	FAC		TAC		*P* value
	Mean	SD	Mean	SD	
Function status[a]					
Physical	57.31	21.17	50.4	23.76	0.002
Role	66.27	32.98	60.13	34.89	0.006
Emotional	56.26	30.1	50.69	30.84	0.007
Cognitive	72.27	30.18	69.38	27.47	0.02
Social	69.61	31.38	64.19	32.95	0.002
Global health status/QOL	65.29	25.87	58.11	24.28	<0.001
Symptoms[b]					
Fatigue	41.74	28.15	46.94	26.91	0.006
Nausea and vomiting	23.93	28.31	16.39	28.37	<0.001
Pain	33.19	30.11	37.48	28.25	0.003
Dyspnea	17.91	25.21	16.25	27.05	0.05
Insomnia	43.70	39.65	47.12	40.65	0.011
Appetite loss	26.84	33.89	22.69	36.29	0.05
Constipation	18.84	30.98	16.85	29.34	0.06
Diarrhea	3.92	19.18	9.80	11.34	0.002
Financial difficulties	50.98	36.35	56.87	32.81	0.008

[a] A high score represents a better level of functioning

[b] A high score represents a worse level of symptoms

particularly patients in the TAC group. It was found that they had worse economical problems (upper mean) in comparison to the FAC group.

Table 5 Toxicity in TAC and FAC at the sixth session of chemotherapy

Toxicity	Regimen				*P* value
	TAC (out of 32)		FAC (out of 68)		
Alopecia	28	87.5	55	80.9	0.091
Amenorrhea	29	90.6	52	76.5	0.009
Cardiotoxicity	1	3.1	2	2.9	0.921
Anemia	11	34.4	12	17.6	0.02
Febrile neutropenia	8	25	2	0.9	<0.001
Hypersensitivity reaction	2	6.25	4	5.9	0.887
Mucositis	16	50	45	66.2	0.058
Hyper pigmentation	25	78.1	28	4.2	<0.001
Neurologic toxicity	5	15.6	–	–	<0.001
Edema	16	50	14	20.6	<0.001

Table 5 showed that the average reported cases of amenorrhea, anemia, febrile neutropenia, hyper pigmentation and nail discoloration, neurologic toxicity and edema in TAC arm were significantly higher than in patients in FAC group. But there were no significant difference between the two chemotherapy regimens in other cases such as alopecia, cardiotoxicity, hypersensitivity reaction and mucositis.

Discussion

Each type of cancer produces particular symptoms. Their symptoms may include fatigue, mental and psychological disorders and denial. Patients may suffer from a lack of self-esteem as a result of dysfunction of limbs and be affected by the length of the disease [13]. All of these symptoms, along with the specific side effects of chemotherapy can undoubtedly alter the patient's quality of life. The major limitation of this study was that, we were not able to design a double-blind clinical trial study for this research because of ethical issues.

This study observed in great detail, the patient's QOL in two chemotherapy regimens: TAC and FAC. The results show that, the use of TAC as an adjuvant therapy in most aspects was accompanied by more side effects. These TAC patients had a higher range of side effects which included: amenorrhea, anemia, febrile neutropenia, hyperpigmentation and nail disorder, neurologic toxicity, edema, fatigue, pain, insomnia and diarrhea. These effects may be attributed to the lower mean score regarding QOL in TAC arm during chemotherapy cycles.

Rom et al. [14] showed that during five cycles of chemotherapy treatment using TAC, there was a vast increase in side effects such as constipation, nausea, stomatitis,

fatigue and alopecia. Martin et al. [15] produce a significant report regarding particular side effects as a result of TAC. These included amenorrhea, febrile neutropenia, fatigue, diarrhea, edema, neurologic toxicity, nail disorder and allergy. The findings of this particular study have many similarities with our study.

The most significant side effects related to a TAC regimen, observed in a study by Boer et al. [16] were: neutropenia, febrile neutropenia and anemia. However, in spite of increased incidence of febrile neutropenia there were no increase in infection and death because of sepsis. Martin et al. [17] pointed to fatigue, asthenia, diarrhea, edema and pain as the most common side effects of TAC significantly but in this study, unlike ours', the mean of nail disorder, nausea and vomiting was not statistically significant.

In other studies such as Brain in 2008 [18], breast cancer international research group (BCIRG) in 2005 [15] and the study of Birmingham university UK in 2004 [19], the rate of neutropenia and febrile neutropenia in TAC arm was higher significantly. Moreover, Voga et al. (2005) showed that grade 3, 4 neutropenia and febrile neutropenia in the TAC group were significantly more than FAC but in this study grade 3,4 neutropenia and cognitive heart disease were not statistically significant [20]. Furthermore, Martin [9] in another study on node-negative breast cancer reported that the mean of febrile neutropenia, fatigue, asthenia and, diarrhea in TAC was more than FAC which was statistically significant.

Based on the results of this study and comparison with other studies, it was discovered that there were more side effects related to TAC than FAC significantly. Neutropenia and febrile neutropenia were found to be most prevalent in the TAC group and this finding corresponds with most other studies, Docetaxel is the only transitive agent in TAC regimen that is accompanied with common side effects as recognized by previous medical texts. The side effects included fatigue (in 80% cases), increased risk of infection due to a reduction in white blood cells, tiredness and breathlessness due to a reduction in red blood cells, anemia, nosebleeds, bleeding gums due to a reduction in platelets, edema (in 50% of cases), skin rashes, discolored fingernails, soreness, redness and peeling on the palms of the hands, complete hair loss (in 80% of cases), sore mouth (in 40% of cases), diarrhea (in 40% cases), numbness and tingling of hands and feet, allergic reaction during the infusion (in 25% of cases); and some other occasional side effects such as: feeling or being sick, loss of fertility and amenorrhea, aching muscles and joints, fever and inflammation around the IV site [21]. Taking into consideration this vast range of symptoms, we are able to justify the diverse results found in the studies.

Furthermore, the above results emphasize the statistical significance between TAC and FAC, both in this study and previous studies. In this study we found that, some side effects such as cardiotoxicity, alopecia, hypersensitivity reaction, loss of appetite and mucositis were found not to be statistically significant between the two groups and this also corresponded with other studies. For instance, in both studies by Martin in 2005 and 2006 [15, 17] there was no significant differences for cardiotoxicity, alopecia and loss of appetite. However, the mean of mucositis in the study of node-negative patients in TAC was higher than FAC significantly [9].

In this study, unlike that of Rom study [14], the mean of nausea and vomiting in FAC arm was higher than TAC significantly. The results of this study correlated with the Martin study of 2006 which showed a higher rate of nausea and in his study in 2005 a higher rate of vomiting in FAC group. Although the cause of nausea and vomiting and mucositis is not only as a result of docetaxel in TAC regimen, but can also be followed by cyclophosphamide, adriamicin (in both regimens) and 5-fluorouracil (in FAC) [22–24], these anomalous results are justifiable.

As to the patients' QOL total mean, the results of this study indicate the same score for QOL in node-positive breast cancer at the first chemotherapy session in both groups (74.5 out of 100) and it decreases after 4 months of follow-up (from 74.5 to 64 in TAC and 74.5 to 68 in FAC) with the 95% confidence interval. This was the same as Martin's study in Spain in 2006 on node-positive breast cancer that indicated every type of chemotherapy decreases the domain of HRQOL during the chemotherapy cycle but this fact in TAC regimen was more because of more severe and common side effects in this protocol. However, in this study at 44 weeks of follow-up, this result for TAC reversed completely [17].

Furthermore, this result was reported in the study of Martin in 2005 in which the primary mean score of QOL in node-positive breast cancer with EORTC QLQ-C30 questionnaire in both groups was 72 out of 100. This result at the sixth session of chemotherapy became 62 in TAC compared with 69 in FAC (95% CI) but when the treatment continued after the first session of follow-up, the level of the scores returned to 76 for TAC and 75 for FAC that was even higher than the initial score before adjuvant therapy [15].

In the study of Martin et al. in Spain (2005) [9] carried out on 1,056 patients with node-negative, the above results of QOL were confirmed so that during the chemotherapy cycle the scores of QOL in TAC arm were lower than FAC (95% CI). But after finishing the chemotherapy cycle, there were no statistically significant differences between their QOL between two groups. Also, Voga showed that the scores of QOL in both groups during the chemotherapy cycle decreased but with the next follow-up, the scores returned to the first level as found at the beginning of the study. Meanwhile, the decrease in the QOL scores in TAC arm was just seen temporarily.

Finally, it is considered that according to the medical texts on chemotherapy side effects [21–24] and the results of our study and the others, the side effects related to TAC during six sessions of chemotherapy were more than FAC. As previously mentioned, these side effects are accompanied by other cancer complications such as fatigue, mental and psychological disorders, illness denial, tribulation in patient's intellectual image of her physical status, decrease in all the functional status and economical problems, leading to a profound negative affection the patients' QOL in TAC during the chemotherapy cycle despite having the same grades in both groups at the beginning of the treatment.

According to facts documented in various studies which predicted positive effects like 28% reduction in relapse and 30% decline in death risk after chemotherapy in TAC [25] and in accordance with a transient reduction in the patients' QOL in TAC arm, the serious need for treatment management for those patients who use TAC in order to increase therapy effectiveness is obvious. In this relation, we can consider using prophylactic granulocyte colony stimulating factor (G-CSF) in these patients to reduce neutropenia and the length of febrile neutropenia. In addition, emphasis on education and increment of patients' knowledge before starting the adjuvant therapy for better and more rational encounter with its side effects and underscoring on the transientness of these symptoms. Peer groups who have completed TAC regimen and supportive group like psychiatrics, psychologist and social worker can help them to reach this target.

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Conflict of interest None.

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