RESEARCH COMMUNICATION

Health-Related Quality of Life of Breast Cancer Patients in Iran: Pooled Analysis using Generalized Estimating Equations

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Abstract

Objective: The aim of current study was to evaluate the changes of health-related quality of life (HRQoL) and its clinical, demographic and socioeconomic determinants during chemotherapy and 4 months follow-up in women with breast cancer using a repeated measures framework. Methods and Materials: A double blind cohort study was performed in 100 breast cancer patients given fluorouracil, doxorubicin and cyclophosphamide (FAC) or docetaxel, doxorubicin, cyclophosphamide (TAC) in south of Iran. HRQoL was assessed at baseline, end of chemotherapy and four months thereafter using the QLQ-C30 questionnaire from European Organization for Research and Treatment of Cancer (EORTC). Generalized estimating equations (GEE) was applied for statistical analysis. Results: The mean of age at baseline was 48.5± 10.6. 70% and 14% of patients were married and smokers, respectively, and 20% suffered from another disease besides breast cancer. The results of GEE showed that after control for baseline scores, the HRQoL significantly improved over time. Although, the patients in FAC group had higher scores than the TAC group, the differences also diminished over time. Smoking, marital status and having child affected some scales of HRQoL. None of other variables were significantly related to HRQoL. Conclusion: Although patients in TAC groups had lower level of HRQoL over 8 months follow up, they experienced faster improvement than the FAC group. This implies that in long-term, improvements in TAC group are higher than FAC. Having children was positively correlated with HRQoL. Generally, there were no demographic and socio-economic differences in HRQoL in these patients between the chemotherapeutic regimens.

Keywords: Breast cancer - TAC - FAC - GEE - Iran

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Introduction

As the traditional end points are mainly concentrated on the biologic and physiologic outcomes, their ability in capturing the impact of interventions on patients' health related-quality of life (HRQoL) has been questioned over last decades, especially for the chronic diseases (Lam et al., 2000). Breast cancer is one of these prevailing chronic conditions which adversely affects the HRQoL in the patients and has been the subject of many studies (Perry et al., 2007).

Breast cancer is considered as first prevalent cancer among Iranian women (Sajadi et al., 2002). A recent study reported an age standardized incidence rate of 23.65 per 100,000 females for 2006 in country (Mousavi et al., 2009). Being in advanced stage of disease and affecting by disease at least one decade younger than their counterparts in developed countries translated the breast cancer to a serious health policy concern in the country (Harirchi et al., 2004; 2011).

Trials have shown that adjuvant therapy reduces the risk of recurrence and death from breast cancer (Early Breast Cancer Trialists' Collaborative Group, 2005). Docetaxel with doxorubicin and cyclophosphamide (TAC) and 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) are used as adjuvant therapy in breast cancer. Results of previous study indicated that although adjuvant therapy with TAC was associated with higher adverse effects, it significantly improved the rate of disease-free and overall survival in node-positive breast cancer (Martin et al., 2005[a]).

A double blind cohort study was done to evaluate the effects of these adjuvant therapies on HRQoL in patients with node-positive breast cancer in Iran. Two previous studies used univariate analysis and separately examined the effects of treatments on HRQoL during treatment and four month after that (Bastani et al., 2010; Hatam et al., 2011). To provide a better picture of changes in HRQoL during whole period of study and examine the effects of clinical, demographic and socio-economic characteristics on these changes, a multivariate repeated measures framework was applied in current study.

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Materials and Methods

The details on study design and population were given somewhere else (Bastani et al., 2010; Hatam et al., 2011). In summary, in a double-blind cohort study, one hundred node-positive breast cancer patients were divided into two chemotherapy groups by physicians` decision: TAC (n=32) and FAC (n=68). Study was done between September 2008 and February 2010 in a hospital radiotherapy center in south of Iran.

Patients agreed to participate in study and filled in the QoL questionnaire. The study was approved by ethics committee of Shiraz University of Medical Sciences. HRQoL was assessed using the standard questionnaire of European Organization for Research and Treatment (EORTC QLQ-C30) (Aaronson et al., 1993) at three time points: baseline (before chemotherapy), end of chemotherapy and four months later. This questionnaire was previously translated, validated and used in the Iranian setting (Montazeri et al., 1999; Atef-vahid et al., 2011).

EORTC QLQ-C30 constitutes of different scales. For this study we used total score and scales which a previous study (Kontodimopoulos et al., 2009) reported that affect the patient's utility. These scales include: physical functioning, emotional functioning, cognitive functioning, global health status and insomnia. Except for insomnia, in all other scales a higher score implies a better HRQoL (Fayers et al., 2001).

For statistical analysis, the method of generalized estimating equations (GEE) was used. This model is an appropriate model for analyzing repeated measures data when the average effects of treatments are the focus (Walters, 2009). This method was previously used in examining the changes of HRQoL in breast cancer patients (Richardson et al., 2007; Shi et al., 2011). We used identity link function, exchangeable correlation structure and robust standard error estimator in our analysis.

The scores at four and eight month follow-up were used as dependent variables. Beside the type of treatment (TAC vs. FAC) and time, the patient's characteristics at baseline including: baseline score, age, marital status (married vs. other), having child (yes vs. no), education level (no education, ≤high school diploma and academic), employment status (unemployed vs. employed), smoking status (smoker vs. non-smoker), presence of comorbidities (yes vs. no) and BMI (kg/m^2) were used as explanatory variables. In the marital status variable, other category included single, divorced and widow. A smoker was defined as a person who smoked at least one cigarette per day or has stopped smoking during last three months. Moreover, people who regularly used water pipe were also considered as smoker. For test if effect of treatment is varying over time, an interaction term of treatment and time was included in the model.

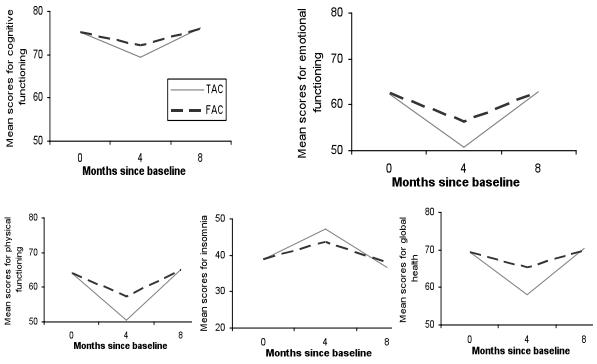

Figure 1. Mean Scores of Scales at First (baseline), Second (end of chemotherapy, 4th month) and Third (four months after chemotherapy) Interviews

Table 1. Clinical, Demographic and Socio-Economic Characteristics of Patients in the Treatment Groups at Baseline.

Variable	TAC (n=32)	FAC (n=68)	Difference p-value
Age (mean ± SD)	46.7 ± 8.23	49.3 ± 11.59	0.23
Married (%)	69	71	0.85
Employed (%)	22	32	0.28
Smoker (%)	16	13	0.75
Presence of comorbidities (%)	16	22	0.45
Education level (frequencies)			
No education	11	22	0.84
High & less	18	39	0.92
Academic	3	7	0.89
BMI (mean ± SD), kg/m^2	26.3 ± 2.10	25.6 ± 2.02	0.11
Emotional functioning (mean ± SD)[a]	62.3 ± 2.45	62.7 ± 2.11	0.39
Cognitive functioning (mean ± SD)[a]	75.1 ± 2.01	75.1 ± 2.64	0.99
Physical functioning (mean ± SD)[a]	64.1 ± 1.96	64.2 ± 0.96	0.79
Global health status (mean ± SD)[a]	69.3 ± 0.98	69.4 ± 1.58	0.89
Insomnia (mean ± SD)[b]	38.8 ± 1.16	38.8 ± 0.85	0.98

*[a]A higher score represents a better functioning, [b]A higher score represents a worse symptom.

Table 2. Predictors of HRQoL in Patients with Breast Cancer using the Generalized Estimating Equations.

	Functioning			Global health	Insomnia	Total score
	Emotional	Cognitive	Physical			
Baseline score	0.6**	0.9**	0.7**	0.7**	0.96**	0.16*
Month	1.6**	0.95**	1.9**	1.2**	-1.5**	1.9**
TAC treatment	-10.8**	-5.9**	-13.9**	-14.7**	8.01**	-6.7**
BMI	-0.01	0.07	-0.03	0	0	-0.17
Smoking	-0.04	- 0.43*	-0.16	-0.15	-0.2	0.23
Having child	0.75*	0.25	0.95*	0.41**	-0.27	1.18
Age	0.02	-0.02	0	0.01	-0.02	0.05
Education						
≤ High school diploma vs. no education	0.36	-0.06	0.06	-0.07	-0.22	0.59
Academic vs. no education	0.15	0.18	-0.04	-0.01	-0.47	-0.42
Employment	0.14	0.01	-0.1	-0.02	-0.05	0
Comorbidity	-0.15	0.03	-0.1	-0.04	0.1	-0.38
Married	-0.33	-0.13	-0.73	-0.41**	0.1	-1.06
TAC treatment * month	1.4**	0.7**	1.8**	1.9**	-1.2**	0.9**
Constant	11**	2.12	4.99	14.7**	13.9**	50.3**

*, **shows the 1% and 5% significant level, respectively

As 58 patients did not know the amount of household income and 7 patients did not like to response to this question, the household income was not included in our analysis. Data were analyzed using STATA version 11 (StataCorp, 2009)

Results

Table 1 shows the clinical, demographic and socio-economic characteristics of patients at baseline. There were no significant differences between patients in two treatment groups. Figure 1 plots the mean of scores over study period. For all scales used in the study, the function deteriorated during chemotherapy and improved during 4 months after.

The results of GEE have been shown in Table 2 for different scales. In all scales, the score at baseline was a significant predictor of scores over study period. All scores were improving over time. Although, patients in TAC group had lower score than FAC in each time point, the speed of improvement was higher in TAC than FAC (interaction between treatment and time). This implies that patients in TAC group have higher deterioration in early month (during chemotherapy), but they experience higher improvement later on, and after some points they will have higher scores than FAC group. Smokers had lower score on cognitive scale than non-smokers. Having child positively affected the emotional functioning, physical functioning and global health scales. Married women had lower score on global health scale than others. Higher BMI, suffering from other diseases and high education were generally related to lower scores, but these were not statistically significant. Older women experienced higher, but statistically non-significant, improvements than their younger counterparts.

Discussion

In the current study, a pooled analysis of HRQoL in patients with breast cancer was done using GEE and related clinical and socio-economic factors were explained. Results showed that HRQoL were deteriorated during chemotherapy and improved later on. In both periods, the speed of changes was higher in TAC than FAC group. It implies that in long-term, the scores in TAC group will exceed the scores in the FAC group.

The improvement of HRQoL over time in patients with breast cancer was also shown in previous studies (Elder et al., 2005; Martin et al, 2005[b]; Larsson et al., 2010). Moreover, the more deterioration in HRQoL during treatment and better improvement in longer-term in TAC group compared with FAC was reported by Martin et al. (Martin et al., 2005[b]). One possible explanation for this is the more severe side effects incurred by TAC during treatment period.

Having children was positively associated with emotional functioning, physical functioning and global health. One explanation for this could be that the women who already had a child are less concern about the effect of disease and treatments on their fertility and hence had higher HRQoL than other women. A recent study (Letourneau et al., 2011) showed that patients who had reproductive loss counsel before treatment and pursued fertility preservation has less regret and better HRQoL than other patients.

Married women had lower score on global health than others. It is possibly due to sexual dysfunction caused by disease and treatment as it was shown that this problem concern a considerable proportion of women with breast cancer (Ganz et al., 1998; Burwell et al., 2006).

Moreover, smoking negatively affected the cognitive functioning in these patients. Although, the negative impact of smoking on survival of breast cancer patients was reported previously (Nguyen et al., 2003), there is a shortage of evidences of the effect of smoking on quality of life in these patients. On the other hand, the negative impact of smoking on HRQoL was reported in other cancer patients (Duffy et al., 2002; Garces et al., 2004). None of other demographic and socio-economic variables were significantly correlated to studied scales.

Using GEE enabled us to examine the changes of HRQoL over time in a longitudinal framework and evaluate the effects of different factors on these changes. On the other hand, the lack of data on the household income did not allow us to examine the effect of this variable on HRQoL.

The results of this study should be interpreted in the light of some limitations. The small number of participants may limit the generalization of the results to other setting, as these patients may not be representative for all Iranian patients specially those who are treated in non-public centers. Moreover, short duration of follow-up avoided to capture long-term benefits of treatments, as these are more interested in chronic diseases. Although, the lack of randomization in allocating patients between the treatment arms may cause selection bias problem in our data, there were no significant differences between two groups in the observed covariates.

In sum, although patients in TAC groups had lower level of HRQoL over 8 month follow up, they experienced faster improvement than FAC group. This implies that in long-term, improvements in TAC group are higher than FAC. We suggest that there is a need of studies with longer follow up and more details data on demographic and socio-economic characteristics to explain HRQoL in these patients more precisely and helping informed decision-making.

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