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COST-UTILITY ANALYSIS OF ADJUVANT THERAPIES FOR BREAST CANCER IN IRAN

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Objectives: The aim of this study was to evaluate the cost-utility of Docetaxel with doxorubicin and cyclophosphamide (TAC) and 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) in node-positive breast cancer patients in the south of Iran.
Methods: A double blind study was done on a cohort of 100 patients suffering from breast cancer with node-positive over 8 months in the radiotherapy center of Namazi hospital, Shiraz-Iran. Health-related quality of life was assessed using questionnaire (QLQ-C30) from European Organization for Research and Treatment of Cancer (EORTC). QLQ-C30 scale scores were mapped to 15D and EuroQol 5D utilities to measure the quality-adjusted life-years (QALYs).Third party payer point of view was applied to measure and value the cost of treatments. Cost data were extracted from hospital and health insurance organizations. Robustness of the results was checked through a two way sensitivity analysis.
Results: TAC was associated with higher deterioration in HRQoL during treatment and higher improvements over 4 months follow-up. On average, the cost of treatment per patient in TAC was 15 times higher than FAC ($p < .001$). In overall, TAC was resulted in lower QALYs and higher cost over study period.
Conclusions: FAC was a dominant option versus TAC in short-term. The higher improvement in HRQoL over follow-up in TAC may not compensate the more intensive deterioration caused during treatment in short-term. The short time horizon of study may limit the generalizability of our findings and, hence, there is a need to conduct long-term economic evaluation studies whenever data is available to inform decision making.

Keywords: Cost-utility, Quality-adjusted life-years, Breast Cancer, Iran

Breast cancer is the most common cancer among women around the world (22). It was estimated that 129,300 women died due to breast cancer in Europe in 2008 (6). Previous studies reported breast cancer as first prevalent cancer among Iranian women (19). A recent study reported an age standardized incidence rate of 23.65 per 100,000 females for 2006 in the country (16). The results of burden of disease survey showed that mortality rate of breast cancer was 2.7 per 100,000 women population and estimated 16,040 years life lost in the twenty-three provinces of country in 2003 (17). Moreover, the examination of breast cancer trend over 20 years showed that despite relative improvement in patients' status, most patients are in advanced stage of disease in country (8). In addition to these, it was reported that breast cancer affects women at least one decade younger than their counterparts in developed countries (7) and this may lead to longer duration of living with disease and in turn, higher expenditures for patients, their families, and society. Hence, prevention and treatment of breast cancer with cost-effective strategies should be considered as a health priority in Iran.

Trials have shown that adjuvant therapy reduces the risk of recurrence and death from breast cancer (5). There are different therapeutic regimens which are used as adjuvant therapy in breast cancer. Docetaxel with doxorubicin and cyclophosphamide (TAC) and 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) are two of these regimens. Comparison of TAC with FAC in a randomized controlled trial showed 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 (14).

The results of recent studies in Iran showed that although TAC had a more negative impact on QoL during chemotherapy, it created a higher improvement than FAC during 4 months since the end of treatment (3;9). TAC, however, is expected to be more costly than FAC, possibly due to the management of its side effects.

To determine the cost-utility of TAC versus FAC in Iranian healthcare system, we performed an economic evaluation study using data gathered in a clinical setting in the south of Iran.

METHODS

Patients and Treatment

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 the south of Iran. Decision on allocating patients between two groups was based on severity of disease and patients who were in more advanced stage of disease usually received the TAC regimen and randomization

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was not applied. However, the patients and researchers were blind to this allocation.

Patients in TAC arm received 75 mg/m^2 docetaxel, 50 mg/m^2 doxorubicin, 500 mg/m^2 cyclophosphamide intravenously (IV) in each session for six times every 3 weeks that prolonged approximately 4 months. During same period, participants in FAC arm received 500 mg/m^2 5-flurouracil, 50 mg/m^2 doxourbicin, and 500 mg/m^2 cyclophosphamide. Patients were followed during 4 months after completing the chemotherapy cycle by their physicians monthly except those who needed more care in the hospital.

Patients gave their consent to participate in study and filled in QoL questionnaire. The study was approved by ethics committee of Shiraz University of Medical Sciences. No severe and serious co-morbidities were reported during the chemotherapy cycle that made patients quit their treatment or change their protocols; in addition there were no cases of death in study period possibly due to they were early stage breast cancer patients.

Inclusion & Exclusion Criteria

Patients with severe renal failures; hepatic impairments; karnofsky performance status less than 70; age older than 75 years; and all the cases of metastasis and node negative were excluded.

All patients younger than 75 years with node-positive (>1) were included.

Outcome Measurement

Quality-Adjusted Life Years (QALY) was used as outcome measure. Details on measuring the health related quality of life (HRQoL) were described elsewhere (3;9). In summary, before treatment, in last session of treatment, and 4 months after the end of chemotherapy the HRQoL was assessed using the standard questionnaire of European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) (1). As the scores in EORTC QLQ-C30 are not utility-based, these scores were mapped to 15-D (20) and EuroQoL 5D (EQ-5D) (4) using equations in Kontodimopoulos et al. (10) which were previously applied in another economic evaluation study (21). Then, differences in utility scores between different points of time (0, 4, and 8 months) were calculated and multiplied in related time period to get QALY gained for each arm.

Cost Measurement

The costs were identified and measured from third-party payer perspective. Thus, only the direct medical costs of treatment and follow-up were considered. These include adjuvant therapy, other relevant drugs, physicians` visits, consultation with the other specialists, hematological and radiological exams, and admissions in the hospital because of treatment's side effect. A checklist was designed to gather these data from hospitals records and health insurance organizations. The time horizon of study was 8 months, and data was gathered for this period.

All costs are expressed in Iranian Rial (1 Rial = USD 0.0001) and were converted to 2008 price level.

Incremental Cost Effectiveness Ratio

Having measured and valued the costs and outcomes, the incremental cost-effectiveness ratio (ICER) was calculated as follows:

$$ICER = \frac{\text{Cost}_{\text{TAC}} - \text{Cost}_{\text{FAC}}}{QALY_{TAC} - \text{QALY}_{\text{FAC}}}$$

In nominator, the differences in average costs per patient in two arms were calculated. This figure, then, was divided on differences in QALY between two groups to get the cost per QALY gained of TAC compared with FAC.

Sensitivity Analysis

To assess the robustness of the study results, a two-way sensitivity analysis was performed. In consultant with experts in health insurance organization it was decided to change the cost as 10 percent in both groups. At the same time, the improvements in utility scores after treatment (over follow-up) were increased as 25 percent for both groups based on clinicians opinions and literature.

RESULTS

Table 1 shows the demographic and socioeconomic characteristics of patients in baseline. The mean age was 49.29 ± 11.59 and 46.71 ± 8.23 years in FAC and TAC groups, respectively. All patients were members of one of health insurance organization in country and have access to coverage provided by these organizations.

Table 2 shows the costs of health services consumed in both treatment groups. It can be seen from Table 2 that in both groups, chemotherapy drugs constitutes the main component of costs. Moreover, on average, the management of adverse events for a patient in TAC group was approximately five times more costly than counterpart in FAC arm. The total cost of treatment was 39490010.6 Rials (USD 3949) and 2559622.3 Rials (USD 256) per patient during 8 months in TAC and FAC groups, respectively. This differences in cost was statistically significant based on Wilcoxon sum rank test ($p < .001$).

Table 3 shows the mean values of EORTC QLQ-C30 scales which were used to map to 15D and EQ-5D based on regression model from Kontodimopoulos and colleagues (10), before the onset of treatment in two groups. As can be seen from this table, there were no significant differences in HRQoL scores between two groups before the onset of treatment. Corresponding 15D utility weights for these level of HRQoL are equal to 0.746 for both groups ($p = .93$). This figures were 0.720 and 0.718 using EQ-5D in FAC and TAC groups, respectively ($p = .61$).

The mean values of HRQoL scales and corresponding utilities in last session of treatment and 4 months after the end of

Table 1. Clinical and Socioeconomic Characteristics of Patients in Baseline

Variable	TAC ($n = 32$)	FAC ($n = 68$)
Age (mean ± SD)	46.71 (8.23)	49.29 (11.59)
Age groups		
30–39 (frequency)	6	19
40–49 (frequency)	15	24
50–65 (frequency)	10	15
65 and older (frequency)	1	10
Covered by health insurance plan (%)	100	100
Smoker (%)	16	13
Unemployment (%)	78	68
Education		
Under high school (frequency)	22	48
High school (frequency)	7	13
Academic (frequency)	3	7
Suffering from comorbidities (%)	16	22
No. of children		
no child(frequency)	6	5
one (frequency)	3	4
two (frequency)	5	11
three and more (frequency)	18	48

Table 3. The Mean of HRQoL Scale Values Before the Onset of Treatment

QLQ-C30 Scales	TAC ($n = 32$)	FAC ($n = 68$)	p value
Emotional functioning (mean ± SD)[a]	62.70 ± 2.11	62.29 ± 2.45	.39
Cognitive functioning (mean ± SD)[a]	75.13 ± 2.64	75.13 ± 2.01	.99
Physical functioning (mean ± SD)[a]	64.20 ± 0.96	64.12 ± 1.96	.79
Global health status (mean ± SD)[a]	69.40 ± 1.58	69.34 ± 0.98	.85
Insomnia (mean ± SD)[b]	38.80 ± 0.85	38.80 ± 1.16	.98

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

treatment have been reported in Table 4. Utility weights calculated by 15D and EQ-5D showed that patients in TAC arm experienced a higher deterioration than FAC during treatment. However, over 4 months follow-up, the patients in TAC arm had higher improvements in their utility and reached to same level as FAC group.

Utility weights at 4 and 8 months were multiplied in related duration (4 months for treatment period and 4 months for

Table 2. Total Costs (USD) of Treatments Over Study Period

	Cost component	TAC($n = 32$)	FAC($n = 68$)
Adjuvant therapy	Chemotherapy drugs per cycle	119082	7226
	Chemotherapy administration(injection &consumable items per cycle)	1729	3674
Visits during chemotherapy cycle	Radiotherapists visits	436	860
	Consults with the other specialists	30	47
Radiology services	Abdominal & pelvic sonography	285	530
	Chest x-ray	78	137
	Bone scan	327	635
	CT scan	196	394
	Breast sonography	45	80
	Mammography	81	174
	Bone densitometer	56	99
Lab services	Lab services	750	1422
Adverse events	Hospital stay	776	273
	Antibiotics	206	31
	GCSF	1656	571
	Anti nausea, vomiting & diarrhea drugs	90	249
	Anti anemia drugs	66	61
	Other drugs	66	58
Follow up		413	886
Total cost		126368	17405

Table 4. The Mean of HRQoL Scale Values and Corresponding Utilities in Last Session of Treatment and 4 Months Later

			In last session of treatment					Four months after the end of treatment				
			FAC		TAC			FAC		TAC		
Tool	QLQ-C30 Scales	Multiplier*	Scale value[a]	Outcome[b]	Scale value	Outcome	*p* value	Scale value	Outcome	Scale value	Outcome	*p* value
15D	Physical functioning	0.00299	57.31	0.17136	50.40	0.15070		64.89	0.19402	65.10	0.19465	
	Global health status	0.00262	65.29	0.17106	58.11	0.15225		70.03	0.18348	70.46	0.18461	
	Cognitive functioning	0.00198	72.27	0.14309	69.38	0.13737		76.08	0.15064	76.11	0.15070	
	Insomnia	−0.00096	43.70	−0.04195	47.12	−0.04523		37.81	−0.03630	36.57	−0.03511	
	Constant	0.26114	1	0.26114	1	0.26114		1	0.26114	1	0.26114	
	Utility			**0.70470**		**0.65622**	<.001		**0.75298**		**0.75598**	.15
EQ-5D	Physical functioning	0.00508	57.31	0.29113	50.04	0.25603		64.89	0.32964	65.10	0.33071	
	Emotional functioning	0.00313	56.26	0.17609	50.69	0.15866		62.83	0.19666	62.89	0.19685	
	Global health status	0.00546	65.29	0.35648	58.11	0.31728		70.03	0.38236	70.46	0.38471	
	Constant	−0.18143	1	−0.18143	1	−0.18143		1	−0.18143	1	−0.18143	
	Utility			**0.64228**		**0.55054**	<.001		**0.72723**		**0.73084**	.30

Note. * β coefficients from Table 3 in Kontodimopoulos et al. (10). These are used to predict 15D and EQ-5D utility scores from EORTC QLQ-C30.
[a]The mean value of scale in sample
[b]Outcome = scale value x multiplier

follow-up) and then were summed to calculate the QALYs. Using 15D equation, the QALY was equal to 0.471 and 0.486 for TAC and FAC groups, respectively ($p < .001$). These figures for EQ-5D equation were equal to 0.427 and 0.457 ($p < .001$).

Incremental Cost Effectiveness Ratio

The results showed that TAC regimen was more expensive and less effective than FAC over 8 months of study period. This means that there is a dominant option (FAC regimen), and there is no need to calculate the ICER.

Sensitivity Analysis

The two-way sensitivity analysis showed that results were insensitive to changes in cost and utility values. This showed the robustness of the results against uncertainty in variables.

DISCUSSION

The aim of this study was to perform a cost-utility analysis of TAC versus FAC in women with node positive breast cancer. To our knowledge, this is first full economic evaluation study in breast cancer patients in Iran.

Results showed that patients in TAC regimen experienced a more intensive deterioration in HRQoL and utility scores during treatment than FAC ones. This higher deterioration in TAC was caused that despite higher improvements in HRQoL and utility scores for TAC over follow-up, the QALY was lower for TAC than FAC over study period. This observed deterioration of HRQoL during treatment and improving over time is in accordance with other studies in breast cancer (11;13;14).

The cost of treatment per patient in TAC was approximately fifteen times higher than FAC arm. The main cost drivers were chemotherapy drugs in both arms. Moreover, the management of adverse effects in TAC group was more costly than FAC. Similar findings were reported by previous economic evaluation studies (2;12;15;23) over 5–10 years and life time follow-up.

In terms of incremental cost-effectiveness analysis, the results showed that FAC was a dominant option against TAC in the 8 months of study period. This is in contrast to the previous economic evaluation analyses of TAC against FAC (2;12;15;23). For example, Au et al. (2) over 10 years of follow-up found that TAC would lead to a gain of 313 QALY (370 life-years) at an additional 5.8 million Canadian dollars. The main explanation for this difference between current and previous studies is related to differences in time horizon of studies. While the time horizon of our study is 8 months, the previous studies modeled 5–10 years and life time costs and effects of these treatments. It seems that long-term benefits of TAC compensate its more side effects during chemotherapy and, hence, it was cost-effective compared with FAC in previous studies. The lack of data on costs and effects in longer-term limited the possibility of capturing full effect of these treatments over life time by conducting a long-term economic evaluation model for Iran. This restricts the generalizability of our findings.

Although, the nonrandomized and uncontrolled design of the study may cause bias in our results, it makes it closer to routine practice in clinical setting.

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 nonpublic centers. Moreover, the utilities were estimated using mapping and these scores may not represent the utility weights for Iranian patients. In other words, while mapping is increasingly used to measure health state utility values when those are not directly available, these values are subject to uncertainty (21). For example, Rowen et al. (18) found that mapping of SF-36 into EQ-5D is not accurate and reliable for more severe EQ-5D health states. These issues should be considered in interpreting our study. Our results may not be directly transferable to other jurisdictions also due to third party payer perspective and the time horizon.

In summary, there were similarities between current study with previous studies in terms of costs and outcomes of TAC versus FAC during short-term. However, in terms of cost-utility analysis the shorter time horizon of current study was resulted in a different conclusion compared with previous ones. The results of the study showed that FAC was a dominant option compared with TAC in short-term. Indeed, the higher improvements in HRQoL after treatment in TAC could not compensate the deterioration caused during treatment in short-term. We suggest that there is a need for a long-term economic analysis whenever data is available to informed decision making. We hope that current study can bring the interests of policy makers and researchers to conduct economic evaluation studies in healthcare system of Iran.

CONTACT INFORMATION

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CONFLICTS OF INTEREST

Both authors report they have no potential conflicts of interest.

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