RESEARCH COMMUNICATION

Comparison of Three Adjuvant Chemotherapy Regimes using an Extended Log-logistic Model in Women with Operable Breast Cancer

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Abstract

Objective: The main objective of the present study was to compare the effects of three common chemotherapy regimes in terms of disease-free survival (DFS) of breast cancer (BC) patients; the three explored regimes were taxane-based, anthracycline-based and CMF (cyclophosphamide methotrexate and 5-fluorouracil). Materials and methods: In this historical-cohort study, we obtained the information of 62 patients with confirmed BC in non-metastatic stage and followed them for 8 years. All the patients had undergone modified radical mastectomy surgery and had received adjuvant chemotherapy in three medical centers in Tehran, Iran. DFS was considered as the end-point. Afterwards, an extended log-logistic regression model was used to compare these regimes. Results: The mean (SD) age of patients was 49.0 (10.3) years. The median time of follow-up was 20.0 months and the probability of 5-years DFS was 0.48. Survival analysis indicated that the type of chemotherapy (OR(CMF vs. taxane) = 0.33, OR(anthracycline vs. taxane) = 0.74), grade (OR(III vs. I or II) = 0.35), tumor size (OR(>5cm vs. <5cm)= 0.179) and nodal involvements (OR(Yes vs. No)= 0.36) affected DFS. Conclusion: The current study revealed that the efficacy of taxane-based, in terms of DFS, was more than CMF (p = 0.05). Moreover, taxane-based chemotherapy prolonged DFS more than anthracycline-based one although the difference was not significant (p= 0.63). Finally, considering the importance of tumor size, histological grade and number of involved lymph nodes in lengthening DFS, it is crucial to highlight the role of public education and screening programs in order to detect tumor in its early stages.

Keywords: Survival analysis - breast neoplasms - adjuvant chemotherapy - disease-free survival

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Introduction

Breast cancer (BC) is the most frequent cancer among Iranian women, comprising 23.6% of all recorded cases of cancer (Cancer office of center for disease control and prevention, 2007; Sadjadi et al., 2009). Based on (Harirchi et al., 2004), BC in Iranian women occurs 10 years earlier compared to those living in developed countries. Although adjuvant chemotherapy treatments after surgery are among the options women with breast cancer have, the number of studies conducted in Iran in order to determine the appropriate adjuvant therapy is still scarce (Fazl-Ali Zadeh and Hatami, 2004; Bakhtyari and Hajyan, 2007; Kadivar and Bozorgmehr 2007). Moreover, the optimal type of adjuvant chemotherapy is still a matter of debate (Cocconi et al., 2004; Hayes, 2009). Whatever the case, however, adjuvant chemotherapy is believed to increase disease-free survival (DFS) and overall survival (OS) following surgery for BC patients (Early Breast Cancer Trialist Collaborative Group, 1992).

Montemurro and Aglietta (2009) summarized over three decades of adjuvant chemotherapy for BC patients into three eras: first, the era of CMF regime; then, that of anthracyclines; and more recently taxanes. CMF has been a standard regime in Europe since the middle 1970s (Bonadonna et al., 1976). anthracyclines play an important role in adjuvant/neoadjuvant settings. anthracyclines-based chemotherapy proved to be, at least, as effective as CMF (Martin et al., 2003).

National adjuvant breast and bowel project (NASBP) B28 study showed that taxane-based (paclitaxel after doxorubicin plus cyclophosphamide) regime was more effective compared to anthracycline-based (doxorubicin plus cyclophosphamide) one in an adjuvant setting in terms of DFS and OS (overall survival). This advantage of the former regime was notably related to lymph node positive patients. Nevertheless, the results were much more limited for positive hormone-receptor patients (Mamounas et

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al., 2005). Inasmuch as controversial results have been reported regarding the role of adjuvant chemotherapy in positive estrogen receptor (ER) patients (Montemurro and Aglietta, 2009), using complex statistical models to determine the role of ER in the recurrence risk has been recommended instead (Dignam et al., 2009).

In this study, we compared the effect of CMF, anthracycline-based and taxane-based regimes in adjuvant settings after modified radical mastectomy (MRM) surgery in terms of DFS. In so doing and to overcome the complexity related to the effect of ER status, we applied an extended parametric survival model with logistic distribution for logarithm of DFS. It should be mentioned that all the comparisons were adjusted by the tumor size, histological grade, lymph node involvement and ER status.

Materials and Methods

Patients and setting:

The data for this historical cohort study were obtained from three centers (hospitals of Shohadaye Tajrish, Madaen and Shahid Fayyazbakhsh) in Tehran, Iran. All adjuvant chemotherapy conducted in these centers from April 1997 to April 2005 was identified. We constrained our attention to BC women (i) who had undergone modified radical mastectomy (MRM) surgery, (ii) with no metastasis at the time of surgery and (iii) who had undertaken adjuvant chemotherapy for the first time using either CMF, anthracycline-based or taxane-based regimes (as elaborated on in the next subsection). Patients with poor quality data were eliminated from the study. Sixty two patients met these criteria and were included in the subsequent phases of this study.

Treatment regimes:

The three arms of adjuvant chemotherapy were: 1- CMF regime: contains cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2) and 5-fluorouracil (600 mg/m^2) repeated every three weeks × 8 cycles; 2- anthracycline-based regimes: combination chemotherapy regimes containing either (i) doxorubicin plus cyclophosphamide (AC) (60/600 mg/m2) repeated every three weeks × 4 cycles or (ii) 5-fluorouracil (500 mg/m^2) plus AC (50/500 mg/m^2) repeated every three weeks × 6 cycles; 3- taxane-based regimes: combination chemotherapy regimes contain a taxane agent. This can be either (i) AC (60/600 mg/m^2) repeated every three weeks × 4 followed by paclitaxel (175 mg/m^2) repeated every three weeks × 4 cycles or (ii) AC (60/600mg/m^2) repeated every three weeks × 4 followed by docetaxel (75-100 mg/m^2) repeated every three weeks × 4 cycles. Tamoxifen, in a dosage of 20 mg each day, was orally given to all positive ER patients after chemotherapy.

Determination, follow-up and diagnosis:

Tumor characteristics such as node statues, tumor size, histological grade, status of ER and some risk factors of BC were recorded. Tumors were classified according to the tumor-node-metastasis (TNM) system of the American Joint Committee on Cancer (American Joint Committee on Cancer: AJCC 2002, 2002) and Scarff-Bloom-Richardson was used as the grading system (Le Doussal et al., 1989). ER was determined by immunohistochemistry (IHC) method. Our patients were followed up by regular clinical examinations, laboratory profiles, serologic markers (CEA, CA15-3) and imaging evaluations. We recorded the number of days from surgery to the first recurrence/metastasis. The endpoint determined by biopsy, chest X-ray, ultrasound, bone scan, liver sonography and marker rising with physician confirmation. Most of the missing subjects were reached one way or another, mainly through phone calls.

Statistical analysis:

In this three-arm study, we used an extended parametric survival model to compare taxane-based with CMF and anthracycline-based regimes adjusted on some prognosis factors. (Royston, 2001) used log-normal as the suitable model for relapse time of patients with BC and ovarian cancer. It is equivalent to using a normal distribution for logarithm of the survival time. Hazard function of log-normal distribution can decrease over time or initially increase to a peak and then decrease (Kalbfleisch and Prentice, 2002; Kleinbaum and Klein, 2005). Royston (2001) suggested using an extended survival model instead of a simple one. In the context of his studies, Browne (1998) and Browne (2006) utilize extended parametric model with complex parameters. In the current study, we used an extended parametric survival model in which we considered the logistic distribution for logarithm of DFS. While log-normal and log-logistic distributions are similar, the former has the advantage of being a proportional odds model (Klein and Moeschberger, 1997). In our log-logistic distribution, we considered the location parameter as a function of the tumor size (divided into two categories: less than or equal to 5 cm as reference category and more than 5 cm), histological grade (divided into two categories: well or moderately differentiated as reference category and non-differentiated) and involvement of lymph node (divided into two categories: positive as reference category and negative). In addition, we considered the scale parameter as a function of ER status (divided into two categories: negative as reference category and positive). In the ordinary log-logistic model, if patient exposed to a certain factor, odds ratio (OR) of recurrence is constant over the time; nonetheless, it is a function of time in the extended log-logistic model (Kleinbaum and Klein, 2005). This property of extended log-logistic model may overcome the difficulty in ER status (Dignam et al., 2009, Montemurro and Aglietta, 2009). In order to determine the appropriateness of the model and covariates that affected on the shape parameters, we used graphical method (Kleinbaum and Klein, 2005).

Furthermore, using Akaike information criterion (AIC), comparisons were made between the final extended model and two other models (Klein and Moeschberger, 1997). The first model was a simple parametric survival model whose scale was constant, and we used ER in its location parameter. The second model was an extended parametric survival model with ER used in both location and scale parameters. An appropriate model can be

selected based on minimum value of AIC (Klein and Moeschberger, 1997). The software we used to analyze the database was R, Version 2.10.0, which is a programming environment for data analysis and graphics (available free from http://cran.um.ac.ir/bin/windows/contrib/)

Results

The mean (SD) and median of follow-up time after MRM surgery were 26.7 (3.2) and 20.0 months, respectively (ranging from less than a month to 14.7 years). At the end of the study, 67.7% of women had no recurrence or metastasis.

The mean (SD) age of women was 49.0 (10.3), ranging from 26 to 73 years. While we observed a tendency to give taxane-based regimes to women with mean (SD) age 46.7(9.7), anthracycline-based to those with mean (SD) age 47.6 (10.7) and CMF regimes to those with mean (SD) age 54.0 (9.1), it was found that these age differences were not statistically significant (p = 0.09) (Table 1). The total mean (SD) of menarche age was 13.5 (1.5). There were no significant difference among the age of menarche in different adjuvant chemotherapy arms (p = 0.6). Menopause women constituted 50.8% of all the patients in the current study. At the start of the study, the frequency of menopause and non-menopause women was similar (Table1). In addition, there was no significance difference among three arms with respect to the menopause status (p = 0.48). Women who received CMF had had more pregnancies than women in other adjuvant chemotherapy arms (p = 0.01).

Table 2 illustrates that about 44% of the women were treated by anthracycline-based regime after surgery and around a quarter of patients (25.8%) were treated using CMF. Most of the patients were detected with a grade III tumor (40.4%) and only 15.5% of patients were detected

Table 1. Risk Factors of Breast Cancer by the Type of Adjuvant Chemotherapy Regime

Risk factor		taxane-based Mean(SD)	CMF-based Mean(SD)	anthracycline-based Mean(SD)	Total Mean(SD)
Age		46.7 (9.7)	54.0 (9.1)	47.6 (10.7)	49.0 (10.3)
Menarche age		13.7 (1.3)	13.5 (0.9)	13.4 (1.0)	13.5 (1.5)
No. of pregnancies		3.2 (1.8)	4.7 (2.4)	2.2 (1.7)	3.1 (2.1)
		N (%)	N (%)	N (%)	N (%)
Menopause	YES	8 (42.1)	10 (62.5)	13 (50.0)	31 (50.8)
	NO	11 (57.9)	6 (37.5)	13 (50.0)	30 (49.2)
	Total	19 (100.0)	16 (100.0)	26 (100.0)	61 (100.0)

Table 2. Major Characteristics of Patients and their Tumors

parameter		N (%)
adjuvant chemotherapy regime	taxane-based regime	19 (30.6)
	anthracycline-based regime	27 (43.6)
	CMF regime	16 (25.8)
Histological grade	Well differentiated (I)	10 (21.3)
	Moderately differentiated (II)	18 (38.3)
	Non-differentiated (III)	19 (40.4)
Involved Lymph node	Negative	21 (33.9)
	1-3	16 (25.8)
	4-10	14 (22.6)
	> 10	11 (17.7)
Tumor size	< 2	9 (15.5)
	2-5	34 (58.6)
	> 5	15 (25.9)
ER status	Negative	17 (28.8)
	Positive	42 (71.2)

Table 3. Estimation of Coefficients of Extended Log-logistic Model for Disease-free Survival

	Parameter		Coefficient (SE)	p-value	OR (95% CI)
Location	constant		9.04 (0.95)	< 0.01	-
parameter	Type of Adjuvant	taxane-based	Reference	-	-
	Chemotherapy regime	anthracycline-based	-0.29 (0.60)	0.63	0.74 (0.23-2.43)
		CMF	-1.11 (0.57)	0.05	0.33 (0.11-1.00)
	Histological grade	I or II	Reference	-	-
		III	-1.04 (0.39)	< 0.01	0.35 (0.16-0.76)
	Tumor size	≤5 cm	Reference		-
		>5 cm	-1.25 (0.47)	< 0.01	0.29 (0.11-0.72)
	Lymph node	No	Reference		-
	involvement	Yes	-1.01 (0.56)	0.07	0.36 (0.12-1.09)
Scale	constant		0.00 (0.43)	0.99	-
parameter	ER status	Negative	Reference		-
		Positive	-1.06 (0.58)	0.05	-

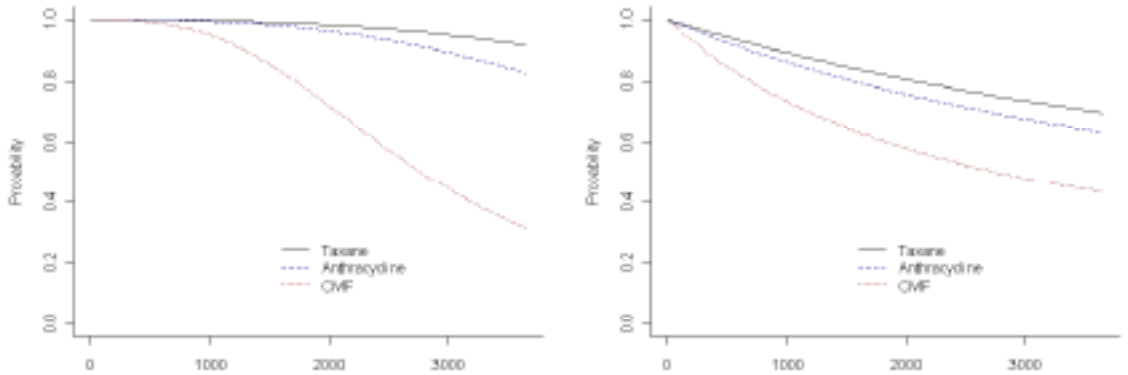

Figure 1. Probability of DFS for ER Positive (left hand) and ER Negative (right hand) in Low-risk Patients by the Tpe of Adjuvant Chemotherapy Regimes

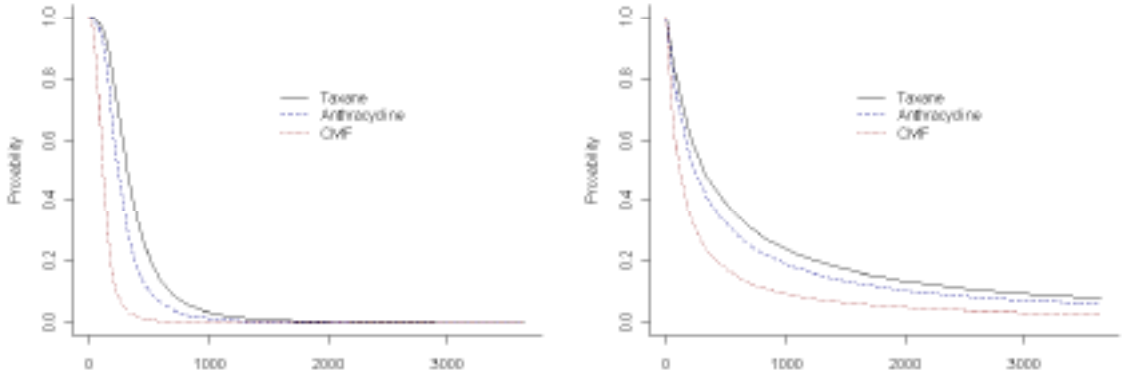

Figure 2. Probability of DFS for ER Positive (left hand) and ER Negative (right hand) in High-risk Patients by the Type of Adjuvant Chemotherapy Regimes

Table 4. The Percentage of Different Patients Without Recurrence/Metastasis of Breast Cancer Over Time

	No. of years following MRM	taxane-based (%)	ER positive anthracycline-based (%)	CMF (%)	taxane-based (%)	ER negative anthracycline-based (%)	CMF (%)
low-risk	1 year	99.98	99.72	98.81	95.85	88.50	82.20
patients*	3 years	99.97	99.34	97.29	94.53	85.21	77.56
	5 years	99.72	93.63	77.10	88.39	71.73	60.3
high-risk	1 year	39.35	2.65	0.62	46.26	22.30	14.69
patients†	3 years	21.94	1.167	0.27	39.18	17.68	11.42
	5 years	2.57	0.11	0.03	22.11	8.641	5.37

* < 5cm, Grade I or II tumor and non-involvement of lymph nodes; † > 5cm, Grade III tumor and lymph node involvement

with a tumor size less than 2 cm. At the time of surgery, more than 40% of women had less than four positive lymph nodes.

As mentioned before, we used an extended log-logistic model to compare the three chemotherapy regimes and compared it with two other models using AIC. The AIC of the simple parametric survival model (the first model), whose scale is constant and in which ER is used in location parameter, was 46.6. In the complex parameter model (the second model), in which ER is used in both location and scale parameters, AIC was 41.59. AIC of our model was smaller in comparison to the first and second models (AIC = 41.29); therefore, it seems to fit better.

Table 3 illustrates the estimation of parameters of extended log-logistic model. The results show that taxane-based regime is significantly more efficient than CMF ($p = 0.05$) in terms of DFS. In addition, the effect of taxane-based regime is more prominent than anthracycline-based regime although it is not significant ($p = 0.63$).

The extended log-logistic model indicates that the odds of recurrence or metastasis in women with a grade III tumor is 0.35 compared to the women with a grade I or II tumor ($p < 0.01$). A tumor of bigger size (> 5cm) results in poorer prognosis in comparison to smaller tumor (< 5cm) (odds ratio (OR) = 0.29; $p < 0.01$). Although not significant ($p = 0.07$), DFS in patients with positive lymph nodes is less than patients with negative lymph nodes. The ER status also has impact on the scale parameter of (log) DFS ($p = 0.05$) (Table 3). A negative coefficient for ER status indicated that ER-positive women who were treated with tamoxifen had better prognoses initially, compared to ER-negative women. However, tamoxifen effect was gradually reversed over time.

Table 4 reveals the DFS percentage of high-risk (tumor size > 5cm, Grade III tumor and positive lymph node involvement) and low-risk (tumor size < 5cm, Grade I or II tumor and negative lymph node involvement) women based on their ER status and the type of adjuvant chemotherapy regimes. All relevant percentages, as can be seen from Table 4, are reported for years one, three

and five following the surgery. For low risk patients, DFS percentage of ER positive patients is higher than that of ER negative patients. However, the ER role gradually changes over time resulting in higher DFS percentages for ER negative patients compared to that of ER positive ones. This role reversal occurs 5 years after the surgery (Table 4). On the other hand, in high risk patients, while DFS percentage of ER positive patients is again higher than that of ER negative patients, the inversion of ER role occurs before the first year following surgery (Table 4).

Figure 1 displays the probability of disease-free survival by ER status in low risk patients. The probability of disease-free survival dropped down after about three years for the ER positive patients treated with CMF. Nevertheless, its probability is more than that of ER-negative patients treated with CMF. The DFS curve for women who received taxane-based regimes was slightly above the curve for those who received anthracycline-based regimes in both ER-positive and ER-negative low-risk patients. The probability of disease-free survival by ER status in high risk patients is illustrated in Figure 2. The probability of DFS in all chemotherapy arms dropped drastically for high-risk patients but not for low-risk patients.

Discussion

In this study, we compared three common adjuvant chemotherapy regimes in terms of DFS, adjusted by some factors using an extended log-logistic model (Kleinbaum and Klein, 2005). The data were collected from three hospitals in Tehran. Adjuvant chemotherapy arms were almost homogenous according to a number of BC risk factors (age at the time of diagnosis: $p = 0.09$, age of menarche: $p = 0.6$ and menopause status: $p = 0.48$) although the number of pregnancies were different in the three arms ($p = 0.01$).

In the model reported in Table 3, the following factors play an important role: (i) the type of adjuvant therapy regime, (ii) the tumor characteristics at the time of diagnosis (tumor size, involvement of lymph nodes and histological grade) and (iii) ER status. In their study, (Hayes et al., 2007) showed that taxane-based regime (addition of paclitaxel to doxorubicin plus cyclophosphamide) may improve disease-free survival compared to anthracycline-based regime (doxorubicin plus cyclophosphamide) in HER2 positive patients. BIG 02-98 randomized trial study, also, suggested that addition of docetaxel into anthracycline-based adjuvant chemotherapy results in the improvement of DFS (HR = 0.86, $p = 0.05$) (Francis et al., 2008). In their meta-analysis that included thirteen studies, (Michele De Laurentiis et al., 2008) showed that regardless of the type of taxane agent, number of involved lymph nodes, ER status, age and menopause status, taxane-based regimes were more efficient than anthracycline-based adjuvant chemotherapy in terms of DFS (pooled HR= 0.83, $p < 0.001$). Similarly, the results we obtained confirmed that, compared to anthracycline-based regimes, taxane-based regimes improved DFS, but the difference between these two types of chemotherapy regimes was not significant (OR (anthracycline-based vs. taxane-based) = 0.74, 95% CI: 0.23-2.43, $p = 0.63$). Furthermore, based on the current study, taxane-based regime is significantly more effective than CMF regime in prolonging DFS (OR (CMF vs. taxane-based) = 0.33, 95% CI: 0.11-1.00, $p = 0.05$).

Early detection of BC is a favorable prognosis factor in increasing survival time (Shen et al., 2005). In their review of PubMed database from 1995 to 2006, Soerjomataram et al. (2008) showed that tumor size, nodal status and histological grade remained the strongest prognosis factors for long-term survival. Similar results were observed in the current study; Table 3 shows that small size of the tumor ($p < 0.01$), low grade of the tumor ($p < 0.01$) and non-involvement of lymph nodes ($p = 0.07$) provide a better prognosis of DFS. However, probably due to the fact that women with larger tumors tend to have more positive lymph nodes (Weiss et al., 2003), the lymph node involvement was not statistically significant. This finding, once more, highlights the conclusion that the early detection of BC improves DFS (Table 4). Some studies have suggested the early detection of BC can result in an almost 30-percent reduction in the mortality rate among BC patients (Alexander et al., 1999; Nystrom et al., 2002). Bakhtyari A, Hajyan (2007) reported that late detection of BC in Iranian women, as compared with its detection in women from developed countries, results in a decrease in DFS. The results of Lamyian et al., (2007)'s qualitative study pointed out that there are some major barriers to facilitation of screening for early detection of BC in Iran. Early Breast Cancer Trialist Collaborative Group (1992) found that the role of ER status on survival probability in BC patients is complicated. It is possible that a factor, initially, have an effect on the risk of recurrence, yet the effect may reverse over time (Dignam et al., 2009; Anderson et al., 2006). Some studies reported that compared to ER negative patients, ER positive patients faced a lower risk in the first several months, but this trend inversed afterwards (Hess et al., 2003; Saphner et al., 1996). Because of the non-constant hazard ratio of ER over time, Dignam et al. (2009) suggested using an extended version of Cox hazard model. In order to take into account the above-mentioned complication, we used an extended model with complex parameters to model the effect of ER status. Based on the AIC, our selected model fits the data better than a simple one. According to this model, ER-positive patients have good prognosis at the early stages of treatment with tamoxifen, but the trend changes afterwards. Table 4 illustrates that for the low-risk patients, the change occurs after five years following surgery. However, the change in trend happens before the first year for high-risk patients. This findings are consistent with the results obtained by Dignam et al. (2009).

In conclusion, this study showed that the type of adjuvant chemotherapy regime and tumor characteristics have direct effects on DFS. In addition, it was demonstrated that the early detection of BC can improve the results of treatment. As a result, the role of raising awareness about breast cancer, self-examination and screening programs is accentuated. Needless to say, considering the limited information about adjuvant chemotherapy in Iran, this study can also prove to be significant as far as it sheds

some new light on the current situation.

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