RESEARCH ARTICLE

Effects of Two Chemotherapy Regimens, Anthracycline-based and CMF, on Breast Cancer Disease Free Survival in the Eastern Mediterranean Region and Asia: A Meta-Analysis Approach for Survival Curves

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Abstract

<u>Background</u>: To compare the effects of two adjuvant chemotherapy regimens, anthracycline-based and cyclophosphamide, methotrexate, fluorourical (CMF) on disease free survival for breast cancer patients in the Eastern Mediterranean region and Asia. <u>Methods</u>: In a systematic review with a multivariate mixed model meta-analysis, the reported survival proportion at multiple time points in different studies were combined. Our data sources were studies linking the two chemotherapy regimens on an adjuvant basis with disease free survival published in English and Persian in the Eastern Mediterranean region and Asia. All survival curves were generated with Graphdigitizer software. <u>Results</u>: 14 retrospective cohort studies were located from electronic databases. We analyzed data for 1,086 patients who received anthracycline-based treatment and 1,109 given CMF treatment. For determination of survival proportions and time we usesb the transformation Ln (-Ln(S)) and Ln (time) to make precise estimations and then fit the model. All analyses were carried out with STATA software. <u>Conclusions</u>: Our findings showed a significant efficacy of anthracycline-based adjuvant therapy regarding disease free survival of breast cancer. As a limitation in this meta-analysis we used studies with different types of anthracycline-based regimens.

Keywords: Meta-analysis - disease free survival curve - multivariate mixed model - adjuvant chemotherapy regimens

Introduction

Breast cancer is considered to be the most common female cancer throughout the world and is the second leading cause of cancer mortality among women. Statistics shows that about one million cases are reported annually; about 60% of them are in developing country. Generally the rate of increase in breast cancer in developing countries is more than in the developed countries. Breast cancer in the west has been linked to obesity, alcohol consumption, diets high in saturated fat, early onset of menarche and late menopause (Katalinic et al., 2009; Arkoob et al., 2010).

The survival rate is one of the most important measures of cancer care and is a valuable tool for comparisons treatments. Also information about survival rates will help us take further preventive and control measures in order to improve prognosis of patients with breast cancer. Breast cancer in the Eastern Mediterranean and Asian women occur at younger ages and is usually presented and diagnosed at later stages. It occurs in younger ages because the young women in this region try to adopt themselves western lifestyle. Presentation is in late stages because of poor education, absence of screening programme, social and cultural barriers and traditional treatment. Survival of breast cancer depends on early detection and treatment. Detection at early stages is very important. The earlier breast cancer is detected, the better chance of survival. The pattern of incidence and mortality of breast cancer are different in different regions, highest incidence rates are found in North America, Northern and Western Europe and Australia, 83-101 cases per 100,000. Lowest rates are in Africa and Asia, 9-33 cases per 100,000 (Katalinic et al., 2009). So it is better choose one region to do a systematic review and meta-analysis. Thus at first we chose EMRO and then to have adequate studies for analysis the rest of asian countries was added. As a country in EMRO in Iran the incidence rate of breast cancer in women was 22 per 100,000, the prevalence in this same population was 120 per 100,000. Stage 1 was diagnosed in 18%, stage 2 was diagnosed in 57% and stage 3 in 25% of cases (this statistics about Iran was reported in 1998) (Mousavi et al., 2007).

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One of the most usual treatments for breast cancer is adjuvant chemotherapy. Adjuvant therapy after breast conservative surgery or mastectomy or modified radical mastectomy reduce the risk of cancer coming back (Arkoob, 2010). Many studies have been done to determine the best chemotherapy regimens for patients, some of studies showed CMF (cyclophosphamide, methotrexate, fluorourical) as a postoperative adjuvant chemotherapy could reduce the risk of recurrence and death rate of breast cancer to 24%. Some of this studies recommended anthracycline-based regimens should be used as a first choice of chemotherapy regimens for breast cancer. However there are no standard regimens that have been shown to provide a survival benefit. In this study we carried out a systematic review in EMRO and Asia to compare the efficacy of the two chemotherapy regimens on disease free survival of patients with breast cancer in studies that reported the survival curves.

The use of quantitative methods to summarize the result of several empirical research studies, or meta-analysis is now widely used in medicine. Meta-analysis usually involves describing the result of each study by means of a numerical index (an estimate of effect size, such as correlation coefficient, mean difference or odds ratio) and then combined these estimates across studies to obtain a summary. Two different statistical models have been developed called fixed effects and random effects model (Larry, 1998). If the outcomes of studies be some endpoints or curves, to consider the correlation between them the more efficient model should be used. In this paper we used the model proposed by (Arends, 2008) to combine the survival curves. However the survival probabilities and its times were obtained by using Graphdigitizer software.

Materials and Methods

Search strategy

All studies published in Persian and English up to the march 30th 2012 relating to the effect of two chemotherapy regimens, Anthracycline-based or CMF, on the disease free survival of breast cancer patients that show the survival curves, had been concerned. Medline, sciencedirect, Chinese information literature database, Japan information on science and technology file on science, Web of science, Sid, Iranpsycho and Chochrane library were systematically searched using appropriate textwords and thesaurus terms for paper relating to breast cancer, use chemotherapy regimens, Anthracycline-based or CMF, and survival analysis. As a limitation this search restricted to the East Mediterranean region and Asia. No limitation was placed on date. In addition to consider the unpublished data, some database like www.controlled_trial.com and www.clinicaltrial.gov had been considered, but no suitable data sets were identified.

Quality assessment

Studies were retained for meta-analysis if they provided disease free survival curve for at least one of the adjuvant chemotherapy regimens, Anthracycline-based or CMF, for breast cancer patients in the countries of EMRO or Asia. Also in all studies the patients who had positive estrogen, progesterone and androgen receptor, had been received hormone therapy. All patients received radiotherapy too. Some studies used radiotherapy before chemotherapy, some studies used after. In some studies the investigator reported the disease free survival curves in some subgroups, in this issue we assumed each subgroup as one independent study. Disease free survival means the length of time after treatment for a specific disease during which a patient survives with no sign of the disease or death.

The following were tabulated, location, date, number of patients and chemotherapy regimens. All studies are retrospective cohort study. Survival curves of all studies are shown too. As mentioned earlier because of this study carried out in East Mediterranean region and Asia so the most patients were younger and their disease presented at a later stage. Also should be added that the patients ranged from 20-73 years old.

Meta analysis

More than 30 papers with relevant content were retrieved of which 14 studies were retained (see Table 1). All curves digitized by graphdigitizer software to determine the survival proportions and its time (month), then prepared data for analysis. In this study we use multivariate random mixed-effect model that relates ln-minus-ln transformed survival proportion to both fixed and random covariates, such as treatment group, ln (time), etc. we assume the following model:

$$Ln[-Ln(S_i)] = X_i\beta + z_i b_i + \varepsilon_i$$
$$b_i \approx N(0,D)$$
$$\varepsilon_i \approx N(0,V_i) \qquad (1)$$

And

Table 1. Characteristics of 14 Studies Retained for Meta-Analysis

Study (year)	Location	Follow-up time	No. patients	Chemotherapy Regimens (No.)	Considerations
Faradmal et al, (2010)	Iran	8-years	18	Anthracycline-based, CMF	All patients are in high risk of breast cancer
Faradmal et al, (2010)	Iran	8-years	25	Anthracycline-based, CMF	All patients are in low risk of breast cancer
Abbas et al, (2011)	Egypt	30-month	67	Anthracycline-based (67)	Patients treated with Radiotherapy postoperative before chemotherapy
Abbas et al, (2011)	Egypt	30-month	150	Anthracycline-based (150)	Patients were treated in a sandwich scheme of RT& CT
Abbas et al, (2011)	Egypt	30-months	50	Anthracycline-based (50)	Patients received RT after CT
Ismaili et al, (2009)	Morocco	100-months	244	Anthracycline-based, CMF (110),(134)	
Ismaili et al, (2010)	Morocco	100-months	288	Anthracycline-based, CMF (162),(126)	Patients treated with ≥2 cycles of concurrent CT with RT
Ismaili et al, (2010)	Morocco	100-months	61	Anthracycline-based, CMF (40),(21)	Patients treated with BCT
Kuru et al, (2005)	Turkey	100-months	349	Anthracycline-based, CMF (91),(258)	Patients have among 1-3 positive nodes
Kuru et al, (2005)	Turkey	100-months	339	Anthracycline-based, CMF (157),(182)	Patients have more than 3 positive nodes
Wang et al, (2011)	China	60-months	687	CMF (117)	
Zhang et al, (2008)	China	42-months	425	Anthracycline-based, CMF (121),(183)	Patients in HER2 over- expressed
Zhang et al, (2008)	China	42-months	235	Anthracycline-based, CMF (68),(72)	Patients in HER2 over- expressed with node-positive
Fang Li et al, (2008)	China	60-months	43	Anthracycline-based (43)	

$$V_i = \begin{pmatrix} V_{i1} & 0 \\ 0 & V_{i2} \end{pmatrix}$$

$$V_{ij} = [^{(SE_{ljk})}/_{(\hat{S}_{ljk}LN(S_{ljk}))}]\sqrt{[\ ^{(SE_{ljk}(1-S_{ljk}))}/_{((1-S_{ljk})S_{ljk})}]}[^{(SE_{ljk})}/_{(\hat{S}_{ljk},LN(S_{ljk}))}] \quad (2)$$

The studies to be combined in the meta-analysis are indexed by l, In each study one or two treatments are considered that be showed by j. The index k counts the time points. S_{ljk} shows the survival proportion in l study for j treatment at k time point in each treatment of each study. S_i is a column vector of S_{ljk} and ε_i is a column vector of residual. SE is the standard error of survival proportion. The β is the parameter vector containing the fixed effects. Z_i is design matrix for random effects. The vector of random coefficient $\boldsymbol{b}_i$ are assumed to be independently and normally distributed with expectation zero and between-studies covariance matrix D and are independent from the ε_i's. The ε_i's just in the same treatment within the same study are expected to be related. The β parameters are estimated with GLS in an iterative manner. Iteration begin with substituting the observed survival proportion in equation (2). Then with new estimated β's the new survival proportion be estimated. This will be repeated until convergence, providing efficient maximum likelihood estimators for β parameters.

By applying the transformation to the survival probabilities, this model makes it certain that the fitted survival probabilities are between 0 and 1 (Dear et al.,1994; Arends et al., 2008). All of these features are available in STATA software and we used it.

Results

By using STATA software the following model was fitted on the data that extract from studies:

$$Ln(-Ln(S_i)) = \beta_0 + \beta_1 treatment_i + \beta_2 Ln(time_i) + b_{0i}$$
$$+ b_{1i}treatment_i + b_{2i}Ln(time_i) + \varepsilon_{i3} \quad (3)$$

Treatment is a dummy variable for chemotherapy regimens, 0=CMF, 1=Anthracycline-based. We allow random effect for the intercept, slope of ln (time) and treatment effect. We used Ln (time) instead of time because Figure 3. showed that the relation between Ln (-Ln(S)) and time was liked a logarithmic function. Also choosing the Ln (-Ln) transformation of the survival proportion and ln (time) as covariate corresponds to a Weibull distribution assumption, If the relation between Ln-minus-Ln of survival proportion and Ln (time) be linear then we can use weibull distribution for the survival time (Arends et al., 2008). The results are given in Table 2 and Table 3.
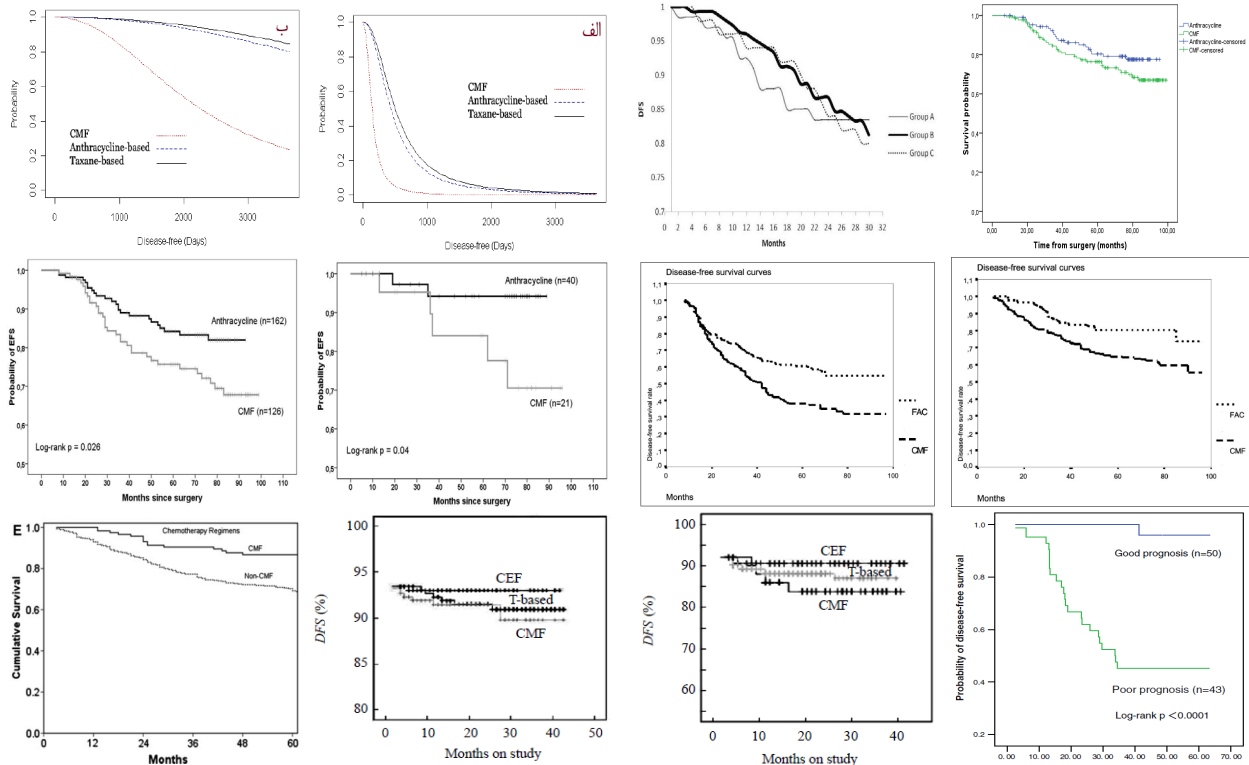

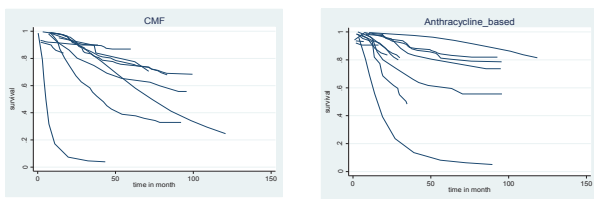**Figure 1. Disease Free Survival of All Studies**

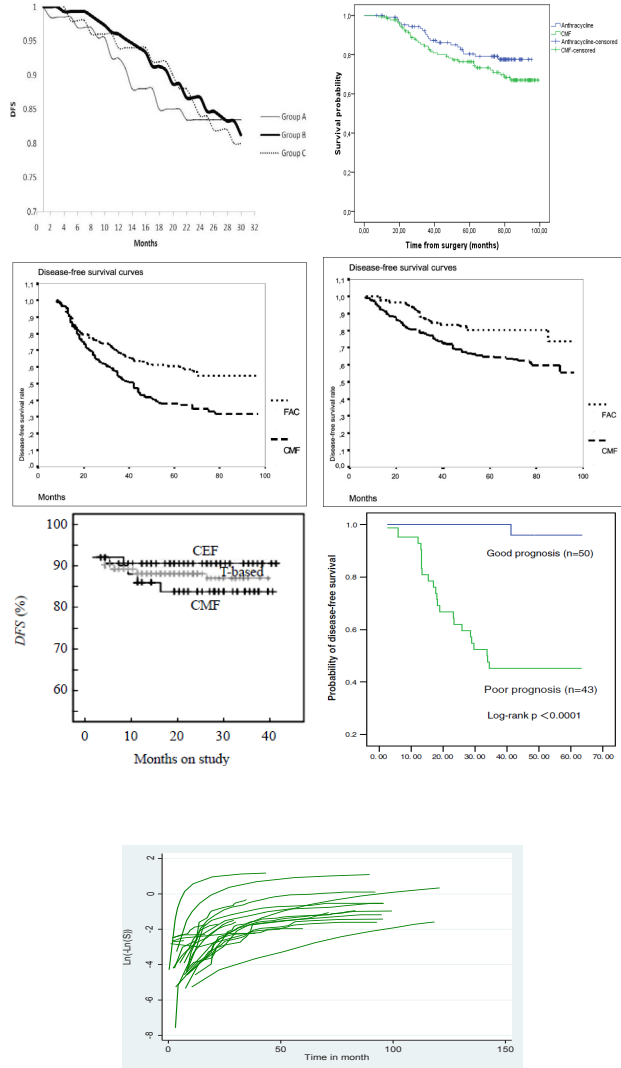**Figure 2. Disease Free Survival Based on Date For Each Chemotherapy Regimens**

Figure 3. Relation between ln(-ln(S)) and Time

Table 2. The Results of Fitting Model (3) for Fixed Part

Regression s coefficients	Estimate	Standard deviation	p-value
Intercept	-4.94	0.53	<0.001
Treatment	-0.57	0.23	0.015
Ln(time)	1.24	0.15	<0.001

Table 3. The Results of Fitting Model (3). (Covariance Parameters).

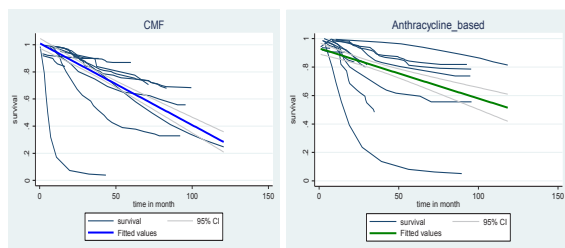| Variance	Estimate	Confidence interval
Intercept	3.13	(1.31 , 7.50)
Treatment	0.51	(0.16 , 1.58)
Ln(time)	0.30	(0.13 , 0.66)
Intercept*traetment	-0.13	(-1.06 , 0.78)
Intercept*ln(time)	-0.59	(-1.30 , 0.11)
Treatment*ln(time)	-0.22	(-0.51 , 0.06)

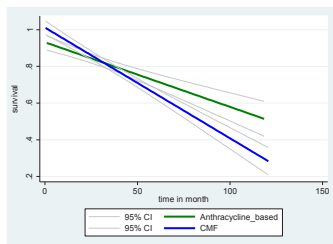**Figure 4. Disease Free Survival Based on Data for Each Chemotherapy Regimens and Fitted Value**

Figure 5. Overall Mean Disease Free Survival Curves (confidence band) of the Two Chemotherapy Regimens

So we have.

$$Ln(-Ln(\hat{S}_i))=-4.94-0.57treatment_i+1.24Ln(time_i)+b_{0i}$$
$$+b_{1i}treatment_i+b_{2i}Ln(time_i) \qquad (4)$$

The regression coefficient of treatment in Table 2 shows significant difference in the benefit of Anthracycline-based treatment over CMF treatment. Mean disease free survival curves with their confidence bands of the two chemotherapy regimens are shown in Figure 4.

According to equation (4) we have:

$$\hat{S}_i=exp(-(exp(-4.94-0.57treatment_i+1.24Ln(time_i)+b_{0i}$$
$$+b_{1i}treatment_i+b_{2i}Ln(time_i))) \qquad (5)$$

So in equation (5) if the coefficient of treatment be more negative then the estimated survival proportion be greater, but according to equation (4) it should be noted that the variation of $Ln(-Ln(S_i))$ by changing the chemotherapy regimen from CMF to Anthracycline-based in a certain time is $(-0.57+b_{1i})$. The b_{1i} for each S_{ijk} is different, so it is possible that the survival proportion varies in favor of another treatment but according to the coefficient of treatment in equation (4) we expect that in the most time especially after 50th month, the survival proportion of patients who received Anthracycline-based regimen be significantly greater.

In Figure 5 we compare the overall mean disease free survival curves of two chemotherapy regimens, also the figure shows significant difference in efficacy of disease free survival in favor of Anthracycline-based regimen. Table 3 shows that between-study covariance matrix differed significantly from zero. It was investigated whether adding terms as interaction between ln(time) and treatment improved the model, but no extension was statistically significant and adding some covariates cause to lost information about covariance matrix.

Discussion

Survival proportions that are reported in each study for each treatment are correlated over time, it means that data have a multivariate nature, so the meta analysis of such data is more complicated. The results of survival analysis are reported as a series of survival proportions at discrete time interval, and time points can be different in each study, so the data are very unbalanced and difficult to analyze with standard methods.

There are many methods that have been proposed for meta-analysis of survival date and survival curves. One of them reduce survival curve to one or more fixed time points, this allows each time point to be analyzed separately. Analyzing on time points separately and carrying out multiple meta-analyses on the same data is not efficient and in more times lead us to inappropriate conclusion. Also it causes to loss the power because in each analysis only a portion of data is used whereas the data are correlated. It can also give rise to a multiple testing problem and interpret the results so difficult. This method also need that the time points at survival curves be identical in all studies. The best approach for meta-analysis of survival data or survival curves is to obtain individual patients data from each study. IPD meta-analysis has big advantages such as the investigator can test the assumptions that has not done in previous studies and the investigators can manage the outlier better. However it is not possible or practical to collect IPD. Obtaining the information of studies and articles is not easy. It seems that obtaining the information of previous studies is one of the most important and effective part of meta-analysis studies especially when the meta-analyst's goal is to combine the survival curves. In the previous meta-analysis studies on survival curves, the investigators had used simulated data or the statistical methods of them were so restricted and had a low power. In this study we used model proposed by Lidia et al. (2008) and graphdigitizer software to digitize the survival curves and obtained the needed information with high precision from survival curves of each study and it seems that the results have a high power by using good transformation and using mixed-effect model in statistical method.

In this paper we use GLS to a multivariate mixed-effect model and the parameters estimated in an iterative manner. Multivariate, because the survival proportions are correlated for each treatment in each study. The modeling approach is very flexible in that the data set does not to

be balanced. This enable we to analyze all available data as provided in the publication, without need to fixed time points (Arends et al., 2008). As a big advantage of this approach is that allows us to use information of studies that use only one treatment. We use ln-minus-ln transformation in combination with ln(time) to interpret the covariate effects as the natural logarithm of the hazard ratio in an cox regression model, when hazard ratio in not constant, the difference in ln (-ln(S)) between two groups can be interpreted as ln (HR) over time (Arends et al., 2008). Our findings in Figure 5 and Table 2 show a significant efficacy from anthracycline-based adjuvant therapy in disease free survival of breast cancer. As a limitation in this meta-analysis we used the studies with different type of anthracycline-based regimens and we just used the studies in Eastern Mediterranean region and Asia. As a similar study Di Leo et al, had done an IPD meta-analysis on the effect of the two chemotherapy regimens, anthracycline-based and CMF, on disease free survival of breast cancer in 2011, they also recorded a significant difference in the benefit of anthracycline-based treatment over CMF treatment in breast cancer patients. Having random effects in our model has a number of important consequence, by using random effect we are modeling variation through variance so it means that the parameters fluctuate around a value with some variance. As noted in results according to equation (4) we expect that in the most time especially after 50th month, the survival proportion of patients who received anthracycline-based regimen be significantly greater

In conclusion, we concluded that the treatment based on anthracycline regimen reduced breast cancer recurrence rate and efficiently improved the disease free survival of breast cancer patients in Eastern Mediterranean region and Asia. By a systematic review and a meta-analysis study we confirmed that the anthracycline-based regimens had more positive effect on disease free survival than CMF regimen.

Acknowledgements

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