Impact of chemotherapy-induced amenorrhea on the prognosis of early breast cancer patients

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Abstract

Purpose: The aim of this work is to find a relatively reliable method to predict the possibility of regaining menses after development of chemotherapy induced amenorrhea (CIA) and to detect if there is an impact of the CIA on relapse-free survival (RFS) and overall survival (OS) in the early stage breast cancer patients
Methods: The chemotherapy-induced amenorrhea (CIA) has been evaluated as a prognostic factor in some studies. These studies were always retrospective and included heterogeneous populations, which mixed hormone-sensitive and resistant tumors as well as hormone-treated and untreated patients.
Results: In this study we retrospectively revised files of premenopausal early breast cancer patients who received adjuvant chemotherapy in Medical Research Institute in Alexandria from the year 2003 to 2008 to find if there is an impact of CIA on relapse-free survival (RFS) and overall survival (OS). Patients who developed CIA had better RFS and OS than those who did not developed CIA, but this difference in RFS and OS was not statistically significant.

Introduction

Breast cancer is the most common malignancy in women, and the second cause of death in women after lung cancer. The American Cancer Society estimated that 209,060 new cases of invasive breast cancer was diagnosed and 40,230 died of breast cancer in United States in the year 2010. [1]
Adjuvant chemotherapy in breast cancer prolongs the DFS and OS, but at the same time it can induce premature menopause by inducing premature ovarian failure. There were many studies that evaluated the effect of adjuvant chemotherapy on ovarian function in breast cancer patients. [2, 3]

Mechanism of ovarian dysfunction caused by chemotherapy:

At birth the human ovary contains approximately 2 millions follicles, but due to continual process of ovulation and atresia this reserve is progressively eroded over time. With aging the primordial follicles population falls bellow a key threshold number, menstrual cycle ceases and natural menopause occurs. Ovarian follicles are vulnerable to agents that cause DNA damage such as chemotherapy, so it reduces primordial follicle reserves, which can result in immediate ovarian failure. [2]
Number of studies have previewed the ovarian histology following chemotherapy to understand the actual mechanism of damage in the ovaries after being exposed to chemotherapeutic agents, one of these studies was carried by Meirow et al. at 1998, that showed that chemotherapy induce pregranulosa cell swelling, marked pregranulosa cell nuclear swelling and primordial follicles architecture disruption with disappearance of the lumen and its oocyte. Positive apoptotic staining was obtained in pregranulosa cells exposed to Cisplatin but not in controls. [4]
Recent studies have initiated mapping the apoptosis signaling pathway underlying germ cell destruction by chemotherapy. A study by Perez et al. has shown that in mice the chemotherapeutic agent Doxorubicin induce apoptosis in the primordial follicles and the first steps of apoptosis occurs in pregranulosa cells. The protein P53 was not required for drug-induced oocyte destruction; however, members of the caspase gene family were required for oocyte death. The pathways of (K^+) regulation showed that potassium efflux during ovarian cell death appears early in oocytes and granulosa cells and may regulate a number of apoptotic events including caspase activity. [5, 6]

Factors affecting occurrence of CIA

The risk for developing CIA is dependent on: patient age, type of chemotherapy and, the total cumulative dose of chemotherapeutic agent. Generally, younger patients are able to tolerate larger cumulative doses of chemotherapy and have a greater likelihood of resumption of menses after therapy is discontinued. [7]
AC; (Adriamycin, Cyclophosphamide) regimen associated with higher rate of occurrence of CIA than CMF regimen, and higher rate of reversibility of CIA. [8]
In a study by Martin et al (2005), CIA occurred more in TAC; (Taxotere, Adriamycin, Cyclophosphamide) arm (61.7%) versus FAC; (Fluorouracil, Adriamycin, Cyclophosphamide) arm (52.4%), P=0.007. [9]

Impact on disease-free and overall survival

The issue of the possible beneficial effect of CIA on long-term survival in premenopausal breast cancer patients remains controversial. [10]

This study investigated the impact of CIA on the prognosis of early breast cancer patients.

Aim of the study

This work aimed to detect if there is an impact of the CIA on relapse-free survival (RFS) and overall survival (OS) in the early stage breast cancer patients.

Material and Methods

The files of all early stage breast cancer patients in Medical Research Institute, Alexandria University, who were: (pre-menopausal, non-metastatic, and received adjuvant chemotherapy) from January 2003 to December 2007, were reviewed and analyzed as follows:

1) Uni-variate analysis:
* The collected data from patients' files were presented in tables and figures.
* Patients Were classified in to two groups; CIA group and no-CIA group.
* Then statistical uni-variate analysis was performed using Chi-square test to investigate the relation between different variables and CIA.

2) Survival analysis:
RFS and OS curves using Kaplan-Meier method were calculated comparing the two groups; CIA and no-CIA group. [11]

3) Multi-variate analysis:
Cox regression model was used to correlate different variables to RFS and OS.

The cut-off points used for categorization were based on previously described cut-off points in the literature. The relapse free survival period measured as the interval between the end of treatment and relapse or death as well as the date of the last follow-up evaluation in patients who had no relapse. Overall survival period was measured as the interval between the beginning of treatment and death and, date of the last follow-up evaluation. [12]

Results:

The patient demographic date included in Table I

There were 326 eligible patients: (non-metastatic, premenopausal, received adjuvant chemotherapy), but only 258 of them had a complete data about the development of CIA in their files.

In the 146 patients showed CIA: 80 patients had permanent CIA, 8 had temporary CIA. And 58 patients were with unknown type of CIA.

The difference in the age between the two groups is statistically significant, (P<0.001). Also the difference in the nodal status between the two groups was statistically significant (P<0.001), but the nodal status is not one of the determinants of CIA, and this difference may be attributed to aggressive tumor biology in the no-CIA group as they are younger in age.

The difference in other variables between the two groups was not statistically significant.

B) Survival Analysis

1- Relapse-free survival

In all patients, the 80 months RFS in the CIA group was 40.6%, and in the no-CIA group it was 36%, but this difference was not statistically significant (P value = 0.130). In a subgroup analysis the hormone-receptor positive patients with CIA had RFS of 79.9%, and those with no CIA had RFS of 72.4% at 80 month, with a trend to better RFS but not statistically significant with P value of 0.375 { figure (I)}.

2- Over-all survival:

Figure (II) shows that 80 months OS in the CIA group was 70%, and in the no-CIA group it was 66.5%, but this difference in OS was not statistically significant, with P value = 0.925.

While, the hormone-receptor positive patients with CIA had an 80 month OS of 73.9%, and those with no CIA had an 80 month OS of 66.6%. There was a trend for better OS by, but also it was statistically not significant with P value of 0.316.

C) Multi-variant analysis

Using Cox Regression analysis, the *CIA was* ***not*** *an independent prognostic variable* in correlation to either RFS or OS, but there were other prognostic variables appear to be independent prognostic variables in correlation to RFS, as the *stage, the number of positive axillary lymph nodes, and Her2/neu* status.

Also, there were other prognostic variables appear to be independent prognostic variables in correlation to OS, as the *tumor size, the number of positive axillary lymph nodes, and ER/PR* status.

The relation between age and timing of occurrence of CIA during chemotherapy:

There is a significant relation between the age of the patient and the timing of amenorrhea with chemotherapy, with younger patients the occurrence of amenorrhea was usually delayed for later cycles, may be due to higher number of follicles in the ovaries of these patients.

Most patients in our study who aged more than 45 years developed CIA after the second cycle chemotherapy, and most patients who were less than 35 years of age developed CIA after the 5th cycle chemotherapy. (Table II)

Discussion

In this study the age of patients who developed CIA ranged between 34-51 years and in patients with no CIA between 29-44 years. This was comparable with the study by Poikonen et al. [13] where the age of patients who developed amenorrhea ranged between 41-56 years, and between 23-44 years in patients with no amenorrhea. There was a significant relation between the age and the CIA in our study with P value less than 0.001, which was also demonstrated in a study done by Parulekar et al. [14] with a P value less than 0.0001, this reflects that the age was one of the determinants of occurrence of CIA as was demonstrated by many other studies. [15, 16] Also in this study there was a relation between the age and timing of CIA, and this relation was illustrated in review article by Jose Benis. [17]

In this study the 5 years RFS in the CIA group was 50.7%, and in the no-CIA group it was 40.6%. This almost matches with the work of Poikonen et al. where the 5 years disease-free survival (DFS) in CIA group was 62% and 44% in the no-CIA group. And in a subgroup analysis of hormonal-receptor positive patients in our study, the 5 years RFS in CIA group was 79.7%, and in no-CIA group it was 72.4%, which matches with work of both Vanhuyse et al. [18] and Parulekar et al.

So, in our study there was a trend toward better RFS in the CIA group of patients but this difference did not reach the statistical significance, this matches with the work of Vanhuyse et al., but in some other studies this difference was statistically significant, as in the study of Poikonen et al., Parulekar et al. and another study done by Pagani et al. which include a very large number of patients which help to illustrate that statistically significant difference. [13, 14, 18]

The 5 years overall survival (OS) in the CIA group in our study was 80%, and in the no-CIA group it was 73.4%. This matches with the work of Poikonen et al. where the 5 years OS in CIA group was 81%, and in the no-CIA group it was 68%. And in a subgroup analysis of hormonal-receptor positive patients in our study, the 5 years OS in the CIA group was 79.3%, and in the no-CIA group it was 66.6%. This matches with the work of Parulekar et al., but did not match with the work of Vanhuyse et al. who found that there was no difference in OS in both groups, which may be due to the poor prognostic criteria of the patients included in his study. [13, 14, 18]

In a multivariate analysis using cox regression to correlate RFS and OS to CIA in our study, CIA was not an independent prognostic variable. This matches with the work of Vanhuyse et al., but did not match with the work of Poikonen et al. where the CIA was an independent prognostic variable for DFS only but not for OS in a multivariate analysis. [13, 14, 18]

Conclusion

The age is one of the determinants of occurrence of CIA; Patients older than 40 years of age have a higher rate of CIA than the patients younger than 40 years. And In older patients CIA occurs early in the course of adjuvant chemotherapy. Early stage breast cancer patients who developed chemotherapy-induced amenorrhea (CIA) tend to have a better relapse-free survival and overall survival than those who did not develop CIA.

Tables

Table 1. Patients Characters in retrospective group

		CIA	No-CIA	
Age	More than 40 years	74 %	**23.5%**	**P = <0.001**
	Less than or equal to 40 years	26 %	**76.5%**	
Path type	IDC	95.9 %	**97 %**	**P = 0.588**
	ILC	1.4 %	**2 %**	
	others	2.7 %	**1 %**	
Chemotherapy	FAC	90.4 %	**95 %**	
	FEC	3.4 %	**1 %**	
	CMF	4.8 %	**2 %**	
	AC	1.4 %	**2 %**	
Stage	I	17.1 %	**16.7 %**	**c^2=20.477 (P= <0.001)**
	II A	26.7 %	**22.5 %**	
	II B	19.9 %	**8.8 %**	
	III A	30.8 %	**28.4 %**	
	III B	5.5 %	**23.5 %**	
Tumor size	T1	38.4 %	**40.2 %**	**c^2=3.702 (P = 0.157)**
	T2	47.3 %	**37.3 %**	
	T3	14.4 %	**22.5 %**	
Axillary LNs	Negative nodes	42.5 %	**24.5 %**	**c^2= 19.386 (P= <0.001)**
	1-3 +ve LNs	21.9 %	**24.5 %**	
	4-9 +ve LNs	29.5 %	**27.5 %**	
	10 and more +ve	6.2 %	**23.5 %**	
Grade	I	1.4 %	**5.9 %**	**c^2= 0.062 (P = 7.318)**
	II	70.5 %	**56.9 %**	
	III	4.8 %	**7.8 %**	
	unknown	23.3 %	**29.4 %**	
Vascular invasion	-ve	19.9 %	**22.5 %**	**c^2= 0.877 (P = 0.262)**
	+ve	35.6 %	**34.3 %**	
	unknown	44.5 %	**43.1 %**	
ER/PR	ER –ve / PR –ve	18.5 %	**25.5 %**	**c^2= 2.982 (P = 0.394)**
	ER +ve / PR +ve	67.1 %	**65.7 %**	
	ER +ve / PR –ve	8.9 %	**5.9 %**	
	ER –ve / PR +ve	5.5 %	**2.9 %**	
Her2/neu	Negative (0 or +1)	7.5 %	**6.9 %**	**c^2= 2.004 (P =0.572)**
	Positive (+3)	6.8 %	**10.8 %**	
	Equivocal (+2)	4.1 %	**2 %**	
	unknown	81.5 %	**80.4 %**	
Relapse		41.1 %	**43.1%**	**c^2= 0.749 (P = 0.103)**

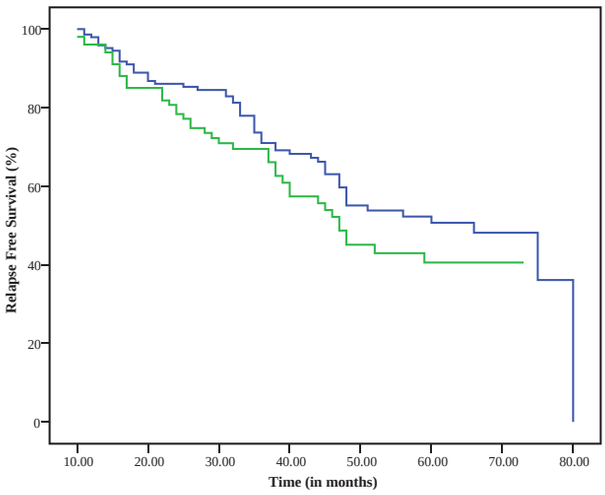
χ^2: Chi square test

Table 2. The relation between age and timing of occurrence of CIA during chemotherapy

	Age					
	Less than 35 years (n = 5)		From 35 to 45 years (n = 81)		More than 45 years (n = 60)	
Timing of amenorrhea	**No.**	**%**	**No.**	**%**	**No.**	**%**
unknown	4	44.45	12	41.5	16	14.8
After first cycle	0	0.0	0	0	1	0.9
After second cycle	0	0.0	2	6.8	42	38.9
After third cycle	0	0.0	0	0	22	20.4
After fourth cycle	1	11.1	3	10.3	24	22.2
After fifth cycle	3	33.35	5	17.3	2	1.9
After sixth cycle	1	11.1	7	24.1	1	0.9
P value	<0.001*					

Figures

RFS in all patients:



RFS in patients with +ve hormone-receptors:

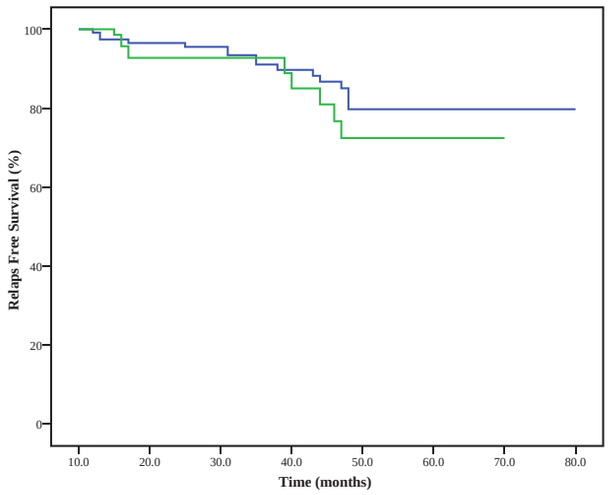
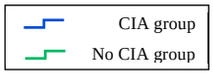
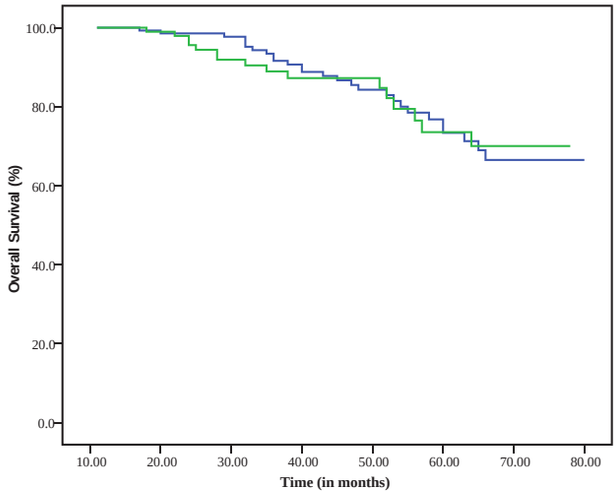


Fig 1: Relapse free survival Kaplan Mayer curve



OS in all patients:



OS in *patients with +ve hormone-receptors*:

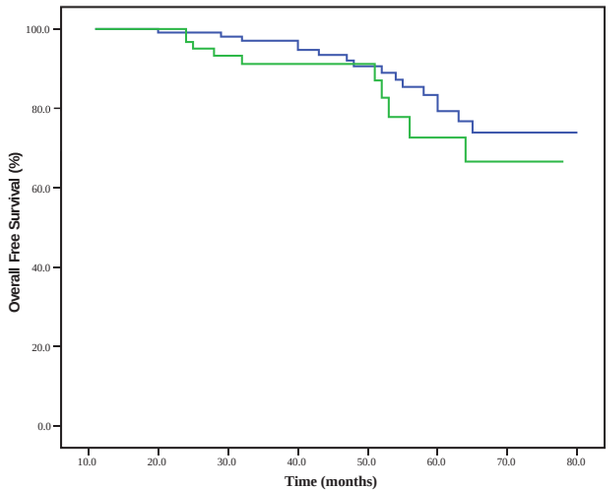


Fig 2: Overall survival Kaplan Mayer Curve

References

1. Jemal A, Siegal R, Xu J, et al. Cancer Statistics 2010, CA Cancer J Clin 2010; 60: 277-300.
2. Meirow D: Ovarian injury and modern options to preserve fertility in female cancer patients treated with high dose radio-chemotherapy for haemato-oncological neoplasia and other cancers. Leuk. Lymphoma 1999; 3: 65-76.
3. Dowsett M, Richner J: Effects of cytotoxic chemotherapy on ovarian and adrenal steroidogenesis in pre-menopausal breast cancer patients. Oncology 1991; 48: 215-20.
4. Meirow D, Nugent D, Epstein M, et al. An in-vitro study of the effects of chemotherapy on human primordial follicles. Hum Reprod 1998 (Absract Book); 13.
5. Perez GI, Knudson CM, Leykin L, et al. Apoptosis-associated signaling pathways are required for chemotherapy-mediated female germ cell destruction. Nature Med 1997; 3: 1228-32.
6. Perez GI, Maravei DV, Trbovich AM, et al. Identification of potassium-dependant and independent components of the apoptotic machinery in mouse ovarian germ cells and granulose cells. Biol Reprod 2000; 63: 1358-69.
7. Wen-Bin Zhou, Hong Yin, Xiao-An Liu, et al. Incidence of chemotherapy-induced amenorrhea associated with epirubicin, docetaxel and navelbine in younger breast cancer patients. BMC Cancer 2010, 10:281.
8. Petrek JA, Naughton MJ, Case LD, et al: Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: A prospective study. J Clin Oncol 2006; 24: 1045-51.
9. Martin M, Pienkowski T, Mackey T, et al. Adjuvant Docitaxelfor node positive breast cancer. Eng J Med 2005; 352: 2302-13.
10. Pagani O, O'Neill A, Castliogne M, Gelber RD. Prognostic impact of amenorrhoea after adjuvant chemotherapy in pre-menopausal breast cancer with axillary node involvement: result of the International Breast Cancer Study Group (IBCSG) trial VI. Eur J Cancer 1998; 34: 632–4.
11. Kaplan E, Meier P: Nonparametric estimation for incomplete observations. J Am Stat Assoc 53: 457-481, 1958.
12. Cox D: Regression model and life tables. J R Stat Soc B 34:187-220, 1972.
13. Poikonen P, Saarto T, Elomaa I et al. Prognostic effect of amenorrhoea and elevated serum gonadotropin levels induced by adjuvant chemotherapy in premenopausal node-positive breast cancer patients. Eur J Cancer 2000; 36: 43–8.
14. Parulekar WR, Day AG, Ottaway JA, et al. Incidence and prognostic impact of amenorrhea during adjuvant therapy in high-risk premenopausal breast cancer: analysis of a National Caner Institute of Canada Clinical Trials Group Study-NCIC CTG MA.5. J Clin Oncol 2005; 23: 6002-8.
15. Petrek JA, Naughton MJ, Case LD, et al: Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: A prospective study. J Clin Oncol 2006; 24: 1045-51.
16. Okanami Y, Ito Y, Watanabe C, et al. Incidence of chemotherapy-induced amenorrhea in premenopausal patients with breast cancer following adjuvant anthracycline and taxane. Breast cancer. 2011;18(3):182-8.
17. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J Clin Oncol 1996; 14: 1718–29.
18. M. Vanhuyse, C. Fournier, J. Bonneterre. Chemotherapy-induced amenorrhea: influence on disease-free survival and overall survival in receptor-positive premenopausal early breast cancer patients. Annals of oncology 2005; 16: 1283.