Incidence of Chemotherapy-Induced Amenorrhea After Adjuvant Chemotherapy With Taxane and Anthracyclines in Young Patients With Breast Cancer

Leila Pourali[1], Ali Taghizadeh Kermani[2, 3], Mohammad Reza Ghavamnasiri[3], Fahimeh Khoshroo[3], Sare Hosseini[3], Mehdi Asadi[2], Kazem Anvari[3]

Abstract

Background: Chemotherapy-induced amenorrhea is one of long term side effects of adjuvant chemotherapy in patients with breast cancer which may interfere with their future reproductive function. Although amenorrhea is well recognized, the actual incidence following taxanes remains uncertain.

Methods: In a cross sectional study, we identified breast cancer patients aged 45 years or younger who were treated with adjuvant anthracycline and taxane-based regimens at three different oncology departments from 2001-2008.

Results: One hundred and nineteen patients met all eligibility criteria and consented to participate in a regular follow up program. The median age at diagnosis was 33.5 years (range, 25-41). Seventy (58%) patients developed amenorrhea for at least 12 months following completion of treatment, and regular menses were maintained in another 49 (42%) patients. No statistically significant association was found between age and development of amenorrhea, although those who experienced cessation of menses were older.

Conclusion: Although taxane containing chemotherapy was associated with higher rate of amenorrhea compared to FAC, this was not statistically significant (P=0.11). Also, treatment with tamoxifen and Estrogen Receptor (ER) positive status was significantly correlated with chemotherapy induced amenorrhea.

Keywords: Breast cancer; Chemotherapy; Amenorrhea; Anthracycline; Taxane

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1. Women's Health Research Center, Ghaem Hospital, Faculty of Medicine , Mashhad University of Medical Sciences, Mashhad, Iran
2. Surgical Oncology Research Center, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
3. Cancer Research Center, Omid Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Corresponding Author:
Ali Taghizadeh Kermani, MD;
Assistant Professor of Radiation Oncology
Tel: (+98) 51 18 02 26 77
Email:TaghizadehA@mums.ac.ir
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Introduction

As the proportion of long term survivors increases because of development of more effective systemic treatment options in breast cancer patients, side effects such as chemotherapy induced amenorrhea becomes more prominent [1, 2].

By definition, Chemotherapy Induced Amenorrhea (CIA) is the cessation of menses within one year of starting chemotherapy and continuing ≥12 months [2]. CIA is well recognized for many chemotherapy drugs especially anthracyclines, but the actual incidence following taxane containing regimens remains uncertain [3].

Several studies demonstrated that the incidence of CIA correlates with some parameters such as chemotherapy type, patient age and hormone therapy [4, 5]. The risk of amenorrhea reported following multi-agent chemotherapy regimen ranges from 21-71% in young women, and 49-100% in those over 40 years of age [3, 6].

This study focused on taxane and anthracycline based regimens, and because of their promising results, they are now more frequently used in breast cancer treatment. In this study, incidence of amenorrhea and its relation to patient's age, taxane or non-taxane type regimen, tamoxifen use, Human Epidermal Growth Factor Receptor 2 (HER-2) and hormone receptor status were analyzed.

Yet, further analysis must answer the following question: Whether anthracycline and taxane induced

amenorrhea has any predictive value for survival of cancer patients?

Materials and Methods

This is a descriptive cross sectional study. The eligibility criteria included patients with documented invasive breast carcinoma, aged less than 45 years who planned to receive chemotherapy and referred to Omid, Ghaem and Imam Reza Radiation Oncology Departments in 2001-2008. They had to participate in our regular follow up visits at least 12 months beyond completion of chemotherapy. Follow up intervals were 3 months during the first 3 years, 6 months up to the fifth year, and then it was performed annually. Those patients who had history of amenorrhea at the beginning of the study, or underwent previous oophorectomy, pelvic field radiotherapy or ovarian ablation with GnRH were excluded from the study. Patients were also allowed to receive tamoxifen if Estrogen Receptor/Progestrone Receptor (ER/PR) status of the tumor was indicated.

Asking about patients' menstrual status at the initiation of chemotherapy and in any visit thereafter was one of our routine questions, so obtaining accurate information about this issue from patients' medical record was not difficult. ER, PR and HER-2 status of the tumors were evaluated by Immunohistochemical (IHC) staining, and according to the references, staining of more than 10% was considered as positive.

To evaluate the role of weight and Body Mass Index (BMI) on CIA, patients were divided into two groups of normal weight (BMI<25), and overweight (BMI≥25). Finally, 119 patients met all eligibility criteria and were enrolled in the study.

Data was analyzed using SPSS version 11.50. The chi-square and independent T-test were used to determine the significance of differences in this study.

Table 1. Incidence of amenorrhea according to chemotherapy type

Chemotherapy regimen	Number of patients with amenorrhea (%)		Total (%)
	No	Yes	
FAC	33 (47%)	37 (53%)	70 (58%)
AC →taxol	16 (32%)	33 (67%)	49 (41%)

Table 2. Incidence of long term amenorrhea according to patient characteristics

Characteristics		Hormone therapy		HER-2* status		ER** status		PR status†		Mean BMI‡
		Yes	No	+	-	+	-	+	-	
Amenorrhea (n=70)	n (%)	45 (77)	25 (41)	40 (65)	30 (51)	39 (68)	31 (50)	36 (66)	34 (47)	27.04
No amenorrhea (n=49)		13 (22)	36 (59)	21 (34)	28 (48)	18 (31)	31 (50)	18 (33)	31 (52)	27.13
P value		0.0001		0.125		0.041		0.113		0.93

* **HER-2:** Human Epidermal Growth Factor Receptor 2
** **ER:** Estrogen Receptors
† **PR:**Progestogen Receptor
‡ **BMI:** Body Mass Index

Results

Out of 732 breast cancer patients, 119 met predefined eligibility criteria, and amenorrhea was detected in long term follow up of 70 (58.82%) cases. The median age at diagnosis was 33.5 years. Incidence of CIA in taxane based vs. FAC regimen was 67.3% and 52.9%, respectively which did not show any significant difference (Table 1). Amenorrhea was significantly more prevalent among patients who underwent hormone therapy and had ER positive tumors, but no correlation was detected between HER2, PR status, tumor stage and patient's BMI (Table 2).

Discussion

Increasing the use of adjuvant chemotherapy in early stage of breast cancer makes long term side effects of treatment more problematic. Chemotherapy-induced amenorrhea is one of these

side effects, which results in vasomotor, psychosocial and cardiovascular dysfunction [6].

However, literature review showed that CIA may have some beneficial effects on hormone receptor positive breast cancers, and that disease free and overall survival may become prolonged in those who experienced persistent amenorrhea [7, 8]. Different types of chemotherapy are associated with different risks of amenorrhea, and the risk also increases with age. Of the 119 patients who were included in the analysis, 49 (42.2%) maintained their regular menses at least 12 months after the completion of the treatment. Therefore, the overall incidence of chemotherapy induced long term amenorrhea was 58.8% (70 of 119 patients). Our study also revealed that AC-T regimen produces amenorrhea more frequently compared to non taxane based (e.g. FAC) protocols, (67.3% vs. 52.9%) although this was not statistically significant. Several studies in the literature used taxane in their regimen reported amenorrhea in range of 51-61% which was more prevalent than non taxane based protocols [2, 9, 10].

Although some reports demonstrated that inclusion of a taxane as part of chemotherapy regimen did not increase the rate of CIA [3, 11, 12].

Although many studies showed older age at diagnosis as an important risk factor for inducing amenorrhea following chemotherapy [4-6], interestingly we found no significant relation between age and CIA in this study. Nevertheless, those patients who developed amenorrhea were older (mean age of 33.5 years). This may be due to limited number of patients compared to other studies [4, 13].

CIA was significantly more prevalent in women with ER positive breast cancer who underwent hormone therapy with tamoxifen, and despite lack of statistical significance, it was also detected to some extent in ER and HER-2 positive cases.

Zhou et al. found age and use of tamoxifen therapy as the two important predictive factors for CIA [14]; and also in the study of Kramer et al. a powerful correlation was found between CIA and tamoxifen in ER positive patients [3].

However, according to some contemporary reports, the actual relation between hormone therapy and CIA remains undefined [15].

In the present study, no significant relation was found between BMI and CIA. Review of the literature also showed contemporary results about CIA and BMI. In Hye-Sue et al. study, CIA was affected by BMI after the second year and those patients with high BMI tended to have persistent amenorrhea, but two other studies demonstrated that BMI had no association with CIA [5, 15].

The retrospective nature of the study and reliance on patients' menstrual history rather than laboratory data for defining menopause were limitations of our study.

Further attempts on prospective data with checking the serum levels of follicle-stimulating and luteinizing hormones and estradiol levels to confirm menopausal status will resolve such limitations.

Conclusion

The addition of a taxane to anthracycline-based chemotherapy did not produce significant chemotherapy related amenorrhea in young patients with breast cancer. According to our study, amenorrhea was partially related to age, but significantly varied with tamoxifen therapy, hormone receptor status and type of chemotherapy regimen.

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Conflict of Interests

The authors have no conflict of interest in this article.

Authors' Contribution

Ali Taghizadeh Kermani and Leila Pourali designed the study, analyzed the data and wrote the paper. Mohammad Reza Ghavamnasiri and Fahimeh Khoshroo contributed to the data entry, literature review and writing-up the process. Sare Hosseini, Mahdi Asadi, and Kazem Anvari contributed to the study design and analysis. All authors read and approved the final manuscript.

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