The Influence of Hormone Therapy on the Development of Pulmonary Fibrosis after Radiotherapy in Patients with Breast Cancer

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ABSTRACT

The aim of the present study is to investigate the effects of hormone therapy on pulmonary fibrosis in patients who received curative conformal radiotherapy for breast cancer. Data of 469 patients were evaluated. Computerized tomography images were evaluated by a radiologist as blindly. The influence of hormone therapy (tamoxifen and aromatase inhibitors), age, menopause, radiotherapy fields, ipsilateral lung volume receiving 5 Gy (V5), ipsilateral lung volume receiving 20 Gy (V20), ipsilateral mean lung dose (MLD) and the effects of taxane group of chemotherapy on pulmonary fibrosis were investigated. The mean age was 51 (range 27-83) years. As hormone therapy, 159 patients (33.9%) used tamoxifen and 253 patients (53.9%) used aromatase inhibitors. A significant relationship was found between both 6th month lung fibrosis and 2nd year lung fibrosis, and V5, V20, MLD, regional lymphatic irradiation and hormone therapy use. More grade 2 fibrosis was detected in the patients who received tamoxifen compared to the patients who received aromatase inhibitors and the control group ($p< 0.001$). No association was found between menopausal status, age, and taxane group chemotherapy and lung fibrosis development. In multivariate analysis, V5, MLD, and using hormone therapy were shown to be independent predictors of the risk of developing fibrosis at both 6 months and 2 years. Use of tamoxifen increases early and late lung fibrosis more than aromatase inhibitors in patients who receive radiotherapy for breast cancer. However, V5, V20, MLD and regional lymph node irradiation also contribute to the prevalence of fibrosis.

Keywords: Breast cancer, Tamoxifen, Aromatase inhibitors, Pulmonary fibrosis

INTRODUCTION

Breast cancer is the most common malignancy in women.[1,2] Adjuvant treatments including radiotherapy (RT), chemotherapy (CT) and hormone therapy are frequently applied to the patients after surgery. Adjuvant RT is applied to all patients after breast-conserving surgery (BCS) and in patients with positive lymph node and T3-4 after modified radical mastectomy (MRM). It has been shown that loco-regional recurrences decrease with postoperative breast irradiation, and overall survival improves in high-risk patients.[1,3,4]

The lungs are one of the organs most sensitive to ionizing radiation and the major dose limiting organ in breast irradiation.[5,6] During RT, part of the lungs is typically located in the field of RT and related toxicity develops.[1] Lung toxicity can be divided into two groups: early (within 6 months) pneumonia and late (after 6 months) pulmonary fibrosis.[1] Radiation fibrosis starts within a few months after RT and progresses over years, usually seen at 6-24th months after RT. Radiological findings may include changes in the RT area, retractions in the lung parenchyma, volume loss, and pleural thickening.[7]

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In addition to its direct toxic effects on target cells, RT can induce inflammatory response, which may lead to pulmonary fibrosis and late morbidity associated with RT.[8] Lung damage is related to a number of factors including the irradiated volume, dose, patient age and anatomy, technique, CT and hormone therapy.[3,8] In some studies, radiation-induced lung damage in breast cancer has been shown with a rate of 4.5-63%.[9] However, in many patients with breast cancer, this damage is asymptomatic due to the small irradiated lung volume and radiation dose.[9]

Adjuvant endocrine therapy has been shown to increase relapse-free survival in estrogen receptor positive patients.[2] Tamoxifen is a selective estrogen receptor modulator and is used especially in patients with hormone-positive breast cancer.[5] Many studies have shown that simultaneous use of RT and tamoxifen increase radiation-induced fibrosis.[5,10,11] Tamoxifen has hormonal effects as well as non-hormonal effects. One of these effects is transforming growth factor β (TGF-β) induction.[5,12] TGF-β is effective in the pathogenesis of radiation-induced pulmonary fibrosis.[5,13,14] TGF-β is a multifunctional regulator of cell growth, epithelial-mesenchymal transition, and differentiation of response to injury.[14] TGF-β cytokine release causes the stimulation of fibroblasts and changes the lung structure by converting tissues into myoblasts. This is followed by an inflammatory response and macrophage accumulation occurs.[7] High plasma concentrations of TGF-before, during and after RT indicate a high risk of pulmonary damage.[10]

Aromatase inhibitors (AIs) have become the standard of adjuvant endocrine therapy in hormone receptor positive postmenopausal women. When the effect of AIs on fibrosis was evaluated, AI was found to be safer than tamoxifen.[5] It has been shown in many studies that it does not increase fibrosis[9] or even decrease it.[4]

In this study, we planned to investigate the effect of hormone therapy on pulmonary fibrosis in patients who received postoperative curative conformal therapy for breast cancer.

PATIENTS and METHODS

Patient Selection

Data of 876 patients who received postoperative RT for curative purposes in our clinic between January 2010 and March 2018 were analyzed. Among these patients, 469 patients who underwent computed tomography at 6 months and 2 years after RT and whose images could be accessed were included in the study. Patients with previously known pulmonary or autoimmune diseases and who could not complete RT treatment for any reason were excluded from the study. Planning tomoghraphy images were used as references. Patients with pre-treatment pulmonary fibrosis were not included in the study. The patients were divided into two groups according to the hormonal therapy they used (tamoxifen and AI). The hormone negative patient group treated according to the same protocol was accepted as the control group.

Ethics committee approval was obtained prior to the study and the study was conducted in accordance with the principles of the latest version of the Helsinki Declaration. Informed consent was not obtained from the patients due to the nature of the study.

This study is approved by the Necmettin Erbakan University Ethical Committee, 17.04.2020...2020/2418.

Treatment

Surgery

Breast conserving surgery or MRM and axillary dissection or sentinal lymph node sampling were applied to the patients.

Systemic Therapy

Four cycles of cyclophosphamide and adriamycin +/– 12 weeks or 4 cycles of taxane group CT were administered as adjuvant or neo-adjuvant therapy according to the stage of the patients. Chemotherapy was applied to 430 (91.7%) of the patients and 240 (51.2%) of them received taxane group CT. 157 (33.9%) patients used tamoxifen 20 mg / day and 253 (53.9%) patients used anastrazole 1 mg / day or letrozole 2.5 mg / day. In the control group, 57 patients (12.2%) did not use hormone therapy.

Aromatase inhibitors were used simultaneously. Tamoxifen, on the other hand, is not used simultaneously in our clinic since it was shown in previous publications to increase pulmonary fibrosis with its simultaneoususe.[5,11]

Radiotherapy

Adjuvant RT was applied to all patients after BCS and in the presence of T3-4 tumor, lymph node positivity, presence of extracapsular extension, lymphovascular invasion or perineural invasion after MRM. Computed tomography (CT) was performed in all patients in the supine position for planning purposes. Target volumes and organs at risk were contoured on the CT. Supra-clavicular irradiation was added to the treatment in patients to be treated with regional lymphatic irradiation. Mammaria interna irradiation was also added in patients with inner quadrant tumors and in patients with a large number of involved lymph nodes. Three dimensional treatment planning and conformal treatment were applied to all patients.6-18 MV direct photon irradiation was performed for the axilla and supra-clavicular region. A dose of 50 Gy, five days a week, 25 fractions were also administered. A boost dose of 10-16 Gy was added in cases undergoing BCS. From the organ doses at risk, ipsilateral lung volume receiving 5 Gy (V5), ipsilateral lung volume receiving 20 Gy (V20) and ipsilateral mean lung dose (MLD) were calculated. All patients were treated with the Eclipse treatment planning system (Varian Medical Systems Inc., Palo Alto, CA).

Radiological Evaluation

The first radiological evaluation was made with the 6th month computed tomography (CT) taken after RTand the second evaluation was made with CT taken at the 2nd year. CT images were evaluated as blindly by the same radiologist. Pulmonary fibrosis grading was performed according to the Radiation Therapy Oncology Group (RTOG) / the European Organization for Research and Treatment of Cancer (EORTC) toxicity criteria.[15] Grade 1 was defined as asymptomatic or mild symptoms and radiological appearance, Grade 2 as mild symptomatic fibrosis or pneumonitis (severe cough), irregular radiological appearance, Grade 3 as severe symptomatic fibrosis or pneumonia, intense radiological changes and Grade 4 as severe respiratory failure, continuous O_2, referred to assisted ventilation.

Statistical Analysis

The data of the study were analyzed with IBM SPSS version 13. Descriptive statistics were used as median (minimum-maximum) and percentage distribution. Pearson's chi-square test was used to compare categorical data. In continuous variables, the normality distribution of the data was evaluated using Kolmogorov-Smirnov / Shapiro-Wilk tests and independent sample test or Mann-Whitney U test was used according to the distribution. For multivariate analysis of factors affecting fibrosis formation, statistically significant or near-significant factors identified in univariate analyzes were included in the logistic regression analysis to determine independent predictors of patient outcomes. Hosmer-Lemeshow test was used for model fit. A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 469 patients were included in this study. All patients had invasive carcinoma. Median age in the study group was 51 (27-83) years. Patient and treatment characteristics are summarized in Tables 1 and 2. As hormone therapy, 159 (33.9%) patients used tamoxifen and 253 (53.9%) patients used AIs. 57 (12.2% - control group) patients did not use hormone therapy. At 6th month, grade 1 fibrosis was observed in 273 (58.2%) patients and grade 2 fibrosis in 18 (3.8%) patients. At the end of the 2nd year, grade 1 fibrosis was observed in 304 (64.8%) patients and grade 2 fibrosis in 37 (7.9%) patients. Grade 3 and 4 fibrosis was not observed in either group. Symptomatic patients were started on corticosteroid therapy. After a few weeks of use, it was gradually reduced and stopped. No additional treatment was given to asymptomatic patients. When early and late fibrosis were evaluated, grade 2 pulmonary fibrosis was detected more frequently at the end of the second year ($p< 0.001$). At the end of the second year, more fibrosis was observed in

Table 1. Patient and treatment charecteristics associated with pulmonary fibrosis at the end of the 6th month

	Pulmonary fibrosis (No) n (%)	Pulmonary fibrosis (Yes) n (%)	p value
Age (y-median)	50 (28-75)	52 (27-83)	0.118
V5 (%-median)	34.71 (4.83-96.69)	36.54 (16.55-82)	0.021*
V20 (%-median)	21.54 (1.46-35.78)	23.20 (6.50-35.98)	0.025*
MLD (Gy-median)	11.58 (1.73-18.62)	12.25 (4.87-23.28)	0.038*
Hormone therapy			
No	34 (19.1)	23 (7.9)	0.001*
Aromatase inhibitors	92 (51.7)	161 (55.3)	
Tamoxifen	52 (29.2)	107 (36.8)	
Menopausal status			
Premenopause	98 (55.1)	141 (48.5)	0.165
Postmenopause	80 (44.9)	150 (51.5)	
Irradiation of the regional lymph nodes			
No	66 (37.1)	79 (27.1)	0.024*
Yes	112 (62.9)	212 (72.9)	
Taxane chemotherapy			
No	84 (47.2)	145 (49.8)	0.579
Yes	94 (52.8)	146 (50.2)	

V5:lung volume receiving ipsilateral 5 Gy, V20:lung volume receiving ipsilateral 20 Gy; MLD: ipsilateral mean lung dose
* Statistically significant

the tamoxifen group compared to the AI and control groups (p< 0.001). When the group receiving AI was examined, grade 2 fibrosis was detected more frequently in the group receiving letrozole in the second year than in the group receiving anastrazole (8.6% vs 1.1%, p= 0.039).

A significant correlation was found between the development of pulmonary fibrosis at 6th month and V5 (p= 0.021), V20 (p= 0.025), MLD (p= 0.038), regional lymphatic irradiation (p= 0.024) and hormone therapy use (p< 0.001) (Table 1). When 2-year fibrosis was evaluated, the relationship between V5 (p= 0.001), V20 (p< 0.001), MLD (p< 0.001), regional lymphatic irradiation (p = 0.003) and hormone therapy use (p< 0.001) was found (Table 2). In both groups, there was no relationship between fibrosis development and age, menopausal status, taxane group CT and surgery type.

In multivariate analyzes, it was shown that using V5, MLD and hormone therapy were independent predictors of the risk of fibrosis development at both 6 months and 2 years.

Multivariate analysis results are shown in Table 3.

DISCUSSION

The present study aimed to evaluate the factors affecting the formation of pulmonary fibrosis and especially the effect of hormone therapy in patients who undergo RT for breast cancer. When the results of 469 patients were examined, it was shown that sequential use of tamoxifen resulted in more pulmonary fibrosis formation than patients using concomitant AIs and not using hormone therapy, and this was more pronounced at the 2nd year. In multivariate analysis, likelihood of pulmonary fibrosis was shown to increase 2.35 fold greater for those using AIs and 4.19 fold greater for those using tamoxifen compared to the control group at the 6th month; at the 2nd year, it was shown that the likelihood of pulmonary fibrosis was 2.79 fold and 5.53 fold greater, respectively. Similarly, V5 and MLD values were shown to increase the risk of pulmonary fibrosis. There was no relationship between age and menopausal status.

Tamoxifen is widely used in hormone-positive women as an adjuvant therapy in the treatment of breast cancer. The use of RT and tamoxifen

Table 2. Patient and treatment charecteristics associated with pulmonary fibrosis at the end of the 2nd year

	Pulmonary fibrosis (No) n (%)	Pulmonary fibrosis (Yes) n (%)	p value
Age (y-median)	50 (28-74)	52 (27-83)	0.345
V5 (%-median)	33.31 (4.83-94.0)	36.59 (16.55-96.69)	0.001*
V20 (%-median)	20.47 (1.46-35.78)	23.43 (6.5-35.98)	<0.001*
MLD (Gy-median)	11.24 (1.73-18.62)	12.34 (4.87-23.28)	<0.001*
Hormone therapy			
No	29 (22.7)	28 (8.2)	<0.001*
Aromatase inhibitors	66 (51.6)	187 (54.8)	
Tamoxifen	33 (25.8)	126 (37)	
Menopausal status			
Premenopause	71 (55.5)	168 (49.3)	0.231
Postmenopause	57 (44.5)	173 (50.7)	
Irradiation of the regional lymph nodes			
No	53 (41.4)	75 (58.6)	0.003*
Yes	92 (27)	249 (73.0)	
Taxane chemotherapy			
No	68 (53.1)	161 (47.2)	0.254
Yes	60 (46.9)	180 (52.8)	

V5: lung volume receiving ipsilateral 5 Gy; V20: lung volume receiving ipsilateral 20 Gy; MLD: ipsilateral mean lung dose
* Statistically significant

has been evaluated in terms of toxicities in many studies. Although no interaction has been shown in pulmonary fibrosis with the simultaneous use of tamoxifen in some studies,[2] most studies have shown that it increases the formation of pulmonary fibrosis.[5,12] Koc et al. showed that pulmonary fibrosis was more prominent (35% vs 13%) with the use of tamoxifen in breast cancer patients treated with adjuvant RT in their prospective study.[11] In another study performed on 328 patients, CT changes were evaluated at 3 months and 1 year after RT. It has been shown that the risk of pulmonary fibrosis increases with the use of adjuvant RT and tamoxifen, but AI and CT with taxan group does not lead to this effect.[9] In their review, McGee et al. compared the use of concurrent or sequential RT and endocrine therapy. They stated that the simultaneous use of AIs is safe. Hovewer, they recommend sequential use of tamoxifen.[16] As the risk of fibrosis increased with simultaneous use of tamoxifen, we used it sequentially, but even in sequential use, more fibrosis was observed compared to AI users and control group. Since there is no difference in 10-year recurrence rates, overall survival and relaps-free survival in the sequential or simultaneous use of tamoxifen[17] we believe that tamoxifen should be used sequentially, taking into account the toxicities.

Aromatase inhibitors have been the standard treatment in women with hormone-positive postmenopausal breast cancer.[18] There are fewer studies of the concomitant use and toxicity of AI and RT. In a meta-analysis, no difference was found when toxicities were compared between AI and tamoxifen.[2] In the animal experiment performed by Yavaş et al.,the authors could not show an increase in the risk of fibrosis with simultaneous use of RT and anastrazole / letrozole.[5] In another experimental study, it was shown that the least fibrosis was in the AIs and RT arm, and even AIs had a protective effect. No difference was found between anastrazole, letrozole and exemestane in terms of fibrosis.[4] In another study conducted in rats, it is emphasized that the use of AI concurrently with RT may be a protective drug on radiotherapy-induced pulmonary fibrosis.[19] In our study, it was shown that AIs made less fibrosis than tamoxifen, but increased

Table 3. Multivariate analysis of factors associated with pulmonary fibrosis (6th month-2nd year)

	Pulmonary fibrosis (6th month)			Pulmonary fibrosis (2nd year)		
	p value	HR	95%CI	p value	HR	95%CI
Age	0.127	1.022	0.994-1.051	0.403	1.013	0.982-1.045
V5	0.003*	0.951	0.920-0.983	< 0.001*	0.940	0.908-0.973
V20	0.096	0.870	0.739-1.025	0.228	0.895	0.748-1.072
MLD	0.022*	1.005	1.001-1.009	0.021*	1.005	1.001-1.010
Hormone therapy						
No	< 0.001*	1		< 0.001*	1	
Aromatase inhibitors	0.007*	2.355	1.266-4.382	0.002*	2.791	1.477-5.275
Tamoxifen	< 0.001*	4.196	2.113-8.332	< 0.001*	5.537	2.694-11.380
Menopausal status	0.538	1.214	0.656-2.247	0.344	1.387	0.705-2.728
Irradiation of the regional lymph nodes	0.146	1.501	0.868-2.595	0.315	1.352	0.751-2.435

V5:lung volume receiving ipsilateral 5 Gy, V20:lung volume receiving ipsilateral 20 Gy, MLD: ipsilateral mean lung dose

* Statistically significant

the risk of fibrosis frequency at the 6th month and 2nd year compared to the control group. In subgroup analyzes, it was shown that letrozole caused more fibrosis than anastrazole. Letrozole has a sensitizing effect on ionizing radiation in breast cancer cells, and this may cause increased toxicity when used simultaneously.[4]

With regional lymphatic irradiation, the lung volume exposed to radiation during RT increases. Radiation-induced pulmonary injury is directly related to irradiated lung volume and supra-clavicular area irradiation within the tangential field.[20] In a study conducted with 613 patients, an increase in the risk of radiation-induced pneumonia was shown with locoregional RT (4.1% vs 0.9%, p= 0.02).[21] In our study, although regional lymphatic irradiation showed an increase in 6 month and 2 year fibrosis risk in univariate analyzes, this relationship was not shown in multivariate analyzes.

There is a strong correlation between radiation pneumonia and radiation fibrosis and dosimetric parameters. V20 and MLD have been shown to be effective in both radiation pneumonia and radiation fibrosis development.[9] However, patients are usually asymptomatic due to the small affected area.

The relationship between smoking and radiation-induced pulmonary fibrosis is controversial. It has been shown to have a protective effect in some studies.[22] In a study of 576 lung cancer patients, they showed that grade 3 and higher pulmonary fibrosis was higher in the non-smokers group.[23]

The most important limitation of our study was its retrospective nature. The results of the patients who underwent computed tomography for any reason were evaluated. TGF-β levels could not be evaluated. We do not know the smoking status of the cases in our study. We could not assess whether this affects lung fibrosis. However, 469 patients with the same technique and the same treatment protocol were evaluated.

Conclusion

Use of tamoxifen increases the occurrence of early and late pulmonary fibrosis more than AIs in patients who received adjuvant RT for breast cancer. V5, V20, MLD and regional lymph node irradiation contribute to fibrosis formation.

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