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ORIGINAL ARTICLE

Effect of Pentoxifylline in Protection the Breast Tissue Against Radiation Injury

Semra GÜNAY,[1] Ömür Yıldız ALAN,[2] Özge KANDEMİR GÜRSEL,[2] Orhan YALÇIN[1]

[1]Department of Breast and Endocrine Surgery, University of Health Sciences, Okmeydanı Training and Research Hospital, İstanbul-Turkey
[2]Department of Radiation Oncology, University of Health Sciences, Okmeydanı Training and Research Hospital, İstanbul-*Turkey*

OBJECTIVE

To investigate the protective effect of pentoxifylline against radiation injury in patients with breast cancer.

METHODS

A total of 82 patients with early-stage breast cancer who underwent breast-conserving surgery and intraoperative electron radiotherapy (RT) as a boost followed by whole-breast RT in the past circa 5 years and completed the full RT dose at least 1 year before were included into this retrospective study. The patients who received prophylactic pentoxifylline (n=44) were assigned to Group A, and those who did not (n=38) to Group B. All cases were evaluated a month (early) and 1 year (late) later, scored according to the Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic scale and analyzed using an independent t-test.

RESULTS

In Group A, the score was 0,1, 2, and 3 in 24,11,seven, and two cases, respectively, in the early period and in 26,10, five, and three cases, respectively, in the late period. In Group B, the score was 0,1, 2, and 3 in 20,10, five, and three cases, respectively, in the early period, and in 15, 12, six, and five cases, respectively, in the late period. The average scores in Groups A and B were, respectively, 0.90/0.86 in the early and 0.65/1.02 in the late period. According to the t-test, there was a significant difference in the late period (p=0.001) in favor of Group A.

CONCLUSION

Penthoxifylline was effective in protection against the radiation injury.

Keywords: Breast cancer; prevention; pentoxifylline; radiation therapy; radiation injury.

Introduction

Nowadays, breast cancer is being increasingly diagnosed at an early stage. As the lifespan of patients with breast cancer becomes longer, the issues associated with the quality of life become more prominent in the daily practice of physicians. Breast-conserving therapy, which is accepted as the standard treatment in early-stage breast cancer, comprises breast-conserving surgery (BCS) and radiotherapy (RT); one of the criteria for the success of this treatment is the cosmetic result.[1] In patients undergoing BCS, protecting the breast skin and tissue from early and late RT side effects is important for physicians. Circulatory impairment is significant because of the skin and superficial tissue changes that occur as a side effect of RT.[1] Inflammation following ischemia may result in fibrosis. Considering the increasing success of early-stage breast cancer treatment and the prolonged life

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www.onkder.org

Dr. Semra GÜNAY
Sağlık Bilimleri Üniversitesi,
Okmeydanı Eğitim ve Araştırma Hastanesi,
Genel Cerrahi Kliniği Meme ve Endokrin Cerrahi bölümü,
İstanbul-Turkey
E-mail: gunaysemra@gmail.com

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expectancy of the patients, poor cosmetic results following RT is an important issue that negatively impacts the quality of life. Several protective or therapeutic methods and medications are used to address this issue. One of them is a theobromine derivative, pentoxifylline, which has hemorheological (blood flow regulating) properties and is used in managing peripheral vascular diseases caused by changes in blood characteristics resulting from various factors. Its most important effect is observed in cases wherein arterial blood density and platelet aggregation is increased, erythrocyte elasticity is reduced, and tissue microcirculation is impaired.[1,2] One of its clinical applications is in cases treated with brachytherapy for breast cancer.[3] Reportedly, 600–1200 mg of pentoxifylline per day for at least 4 weeks ensures a 50%–60% subjective and objective improvement.[3,4] At our clinic, we administer pentoxifylline 600 mg twice daily for 4–5 weeks for the treatment of patients receiving intraoperative electron RT (IOERT) who exhibit comorbidities, such as hypertension, skin sensitivity, and diabetes mellitus, and manifested edema and erythema of the skin during the early treatment period. We observed that despite certain accompanying issues, examination results from the early treatment period of these patients were better compared with those of patients who were not treated with pentoxifylline. Therefore, we planned the present study to investigate the prophylactic effect of pentoxifylline on the damage caused by IOERT.

Materials and Methods

This study was conducted by retrospectively reviewing data recorded in the breast surgery outpatient clinics. Eighty-two out of 98 cases, who underwent BCS and IOERT as a boost since October 2013 and completed their full RT dose at least 1 year before, were included in this study. The patients received an equivalent dose of 10 Gy as a boost during surgery with on average 865 MU (773–954) and 90% reference isodose 6 mEV energy via an administration tube with a diameter of 5.4 cm (4–7); in the whole-breast radiation therapy (WBRT), a total dose of 56-60 Gy RT was administered with a mean of 46–50 Gy (1.8–2 Gy/day at equal doses).

Group A (n=44) included patients aged >50 years with a comorbid disease such as diabetes, vasculitis, hypertension, and those who had a sensitive skin predisposed to atopy. These patients received pentoxifylline 600 mg tablet daily as a preventive agent starting from the day of surgery. Adjuvant RT was initiated approximately 1 month after surgery, and the agent was continued for 8 weeks at the same dose throughout the entire course of RT. The patients in Group B were selected among those who had similar characteristics in terms of age, menopausal status, treatment method, but who did not receive pentoxifylline. Sixteen patients who had caffeine allergy and who did not complete the RT dose and/or 1-year period following the completion of the entire course of RT required to evaluate "late-period results" were excluded from the study.

Table 1 Late effects normal tissue task force-subjective, objective, management, analytic scale (V06.7/2003) for breast cancer radiotherapy: postradition fibrosis

Grade 0	None
Grade 1	Barely increased density/palpable
Grade 2	Increased density and firmness
Grade 3	Marked density, retraction, and fixation

All cases were examined 1 month (early period) and 1 year (late) after receiving the full RT dose, and the "skin-tissue findings" were recorded. The results were scored using the Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic (LENT-SOMA) (V06.7/2003) scale [5], and the results were compared with the t-test (Table 1).

Results

The cases in Group A (n=44) included patients aged >50 years who also had comorbidity, such as sensitive skin with accompanying atopy, diabetes, vasculitis, and hypertension. The mean age was 54 (50–62) years. Twelve patients were premenopausal and 32 cases were postmenopausal. Seventeen cases had hypertension (five of them also had diabetes mellitus and four had vasculitis), 11 had diabetes, three were on a postmenopausal hormone replacement therapy, and skin structure of 13 cases was predisposed to atopy. In Group B, the mean age was 49 (39–59) years, and 16 cases were premenopausal and 22 cases were postmenopausal (Table 2). In Group A, the LENT-SOMA score in the early period was 0 in 24 cases (55%), one in 11 cases (25%), two in seven cases (15%), and three in two cases (5%) in the early period, and the LENT-SOMA score in the late period was zero in 26 cases (59%), one in 10 cases (23%), two in five cases (11%), and three in three cases (7%). In Group B, the LENT-SOMA score in the early period was zero in 20 cases (53%), one in 10 cases (26%), two in five cases (13%), and three in three cases (8%), and in the late period, it was zero in 15 cases (39%), one in 12 cases (32%), two in six cases (16%), and three in five cases (13%) (Table 3, Fig. 1).

Table 2 Characteristics of patients

Group	A (n=44)	B (n=38)
Median age (range)	54 (50-62)	49 (39-59)
Menopause status n: pre-/post-	12/32	16/22
Comorbidity	+	– (none)
Hypertension (HT)	17	–
Diabetes mellitus (DM)	11	–
Vasculitis (V)	4	–
Skin atopy	13	–

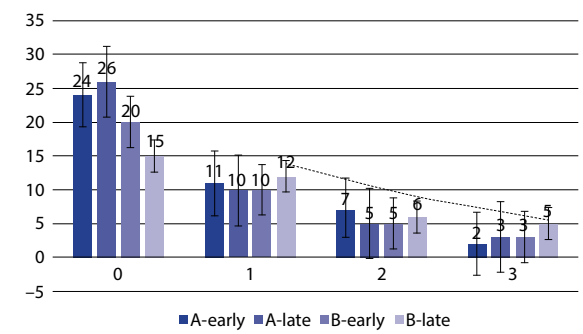

Fig. 1. Early and late period scores of Groups according to LENT-SOMA scale.

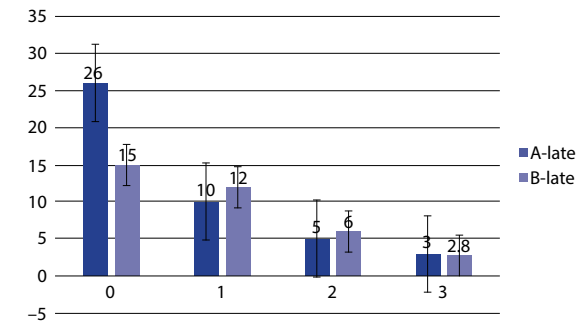

Fig. 2. Significant difference in results between late period of Groups, (p=0.001).

The mean score was 0.90 in Group A and 0.86 in Group B in the early period, and 0.65 in Group A and 1.02 in Group B in the late period. In the statistical analysis with independent t-test, the difference between the score of Group A in the early period and the score of Group B in the early period was not significant (p=0.11), whereas difference in the late period was significant (p=0.001) in favor of Group A (Table 4, Fig. 2).

Discussion

Physicians have a particular concern regarding the unfavorable effects of RT on cosmetic outcomes, which is one of the fundamental criteria of breast-conserving therapy considered to be a standard treatment approach to early-stage breast cancer.[1,5]

It is known that RT has adverse effects on the skin and tissue, depending on the administration area, particularly in patients receiving RT due to breast and head and neck cancer. While a significant number of patients have mild and temporary effects, some of them may be worse and permanent.[5,6] In addition to the effects of RT on the skin, changes occurring in deeper layers are mostly related to the dermis and may lead to permanent damage. These effects can occur hours or months after the exposure to radiation.[6] It is estimated that 85%–95% of cancer patients receive RT, and less than 85% of these patients experience radiation dermatitis. However, less than 10% are serious cases, and treatment may not be sufficient. They adversely affect the

Table 4 Median scores of groups and p-values

Group	A (early/late)	B (early/late)
Median score (Late effects normal tissue task force-subjective, objective, management, analytic)	0.90/0.65	0.86/1.02
p	0.11	0.001

Table 3 Early- and late-period scores of groups according to late effects normal tissue task force–subjective, objective, management, analytic (LENT-SOMA) scale

LENT-SOMA Score	Group A–Early p. n (%)	Group A–Late p. n (%)	Group B–Early p. n (%)	Group A–Late p. n (%)
0	24 (55)	26 (59)	20 (53)	15 (39)
1	11 (25)	10 (23)	10 (26)	12 (32)
2	7 (15)	5 (11)	5 (11)	6 (16)
3	2 (5)	3 (7)	3 (8)	5 (13)

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patient and physician satisfaction and the quality of life.[5,6,7] Therefore, it is important to protect tissues by considering the mechanism of radiation damage.

Ionizing radiation leads to the release of highly reactive free radicals. Inflammation mediated by the peptides, lipids, and DNA-containing cellular molecules occurs in the dermis and epidermis through the reaction triggered by RT above the threshold dose. If the tissue is re-exposed to the same effect before the DNA repair is completed, the tissue perfusion is compromised as a result of thinning and narrowing of the vascular structures, leading to atrophy and fibrosis.[6] These effects do not occur in all cases, and they may be due to the application itself and may be also aggravated by personal risk factors. These risk factors include atherosclerosis, hypertension, vasculitis, diabetic angiopathy, and skin structure.[6,7] They may start after the exposure to radiation, and the threshold dose is approximately 10 Gy.[7,8]

Some scales used by the Radiation Therapy Oncology Group are used to grade the late effects of radiation damage to tissues such as skin, subcutaneous tissue, mucosa, and soft tissue, and deeper structures such as muscles and tendons; however, the LENT-SOMA seems to be more appropriate when evaluating the effects of superficial RT, especially of IOERT.[5,8] We decided to evaluate the results with the LENT-SOMA scale in this study.

The main reason for severe and permanent effects of radiation is the disruption of microcirculation. Pentoxifylline, which enhances treatment by decreasing edema, atrophy, and fibrosis and promoting circulation in the skin and superficial tissues, may also protect against the radiation damage. Pentoxifylline is a member of the methylxanthine class, which includes caffeine and theoriline. It prevents inflammation by inhibiting the leukotriene synthesis and tumor necrosis factor (TNF), a mediator that increases intracellular cAMP and initiates inflammation. It is also a nonselective phosphodiesterase inhibitor. With this action, it contributes to tissue repair and also protects the immune system.[8] Pentoxifylline reduces the blood viscosity by increasing the flexibility of erythrocytes. It promotes the circulation of erythrocytes, not only in subcutaneous tissues, but also in deeper tissue layers. It improves the deformability of erythrocytes (hemorheological effect), reduces blood viscosity, and reduces the platelet aggregation and the potential of thrombus formation. Thus, as blood density decreases, it is possible to reach deeper tissues compared to normal.[9,10] Furthermore, several studies have investigated whether this effect of pentoxifylline increases the effects of RT on the skin and tissue. The experimental study by Öksuz et al.[11] has evaluated the radiation response of Ehlrich breast carcinoma in mice via comparisons with the control group, although the said study identified no RT enhancing effect. On the other hand, numerous studies have shown a reduction in the side effects of RT by pentoxifylline; accordingly, this drug is currently used in the treatment of inflammation-induced impairment of vascular circulation, diabetic nephropathy, post-ERCP edema, all types of vasculitis, newborn sepsis and burns, as well as in the prevention of fibrosis development following RT.[10,12] Pentoxifylline is used in the treatment of diabetic nephropathy, in which the circulation is compromised by inflammation, post-ERCP edema, all types of vasculitis, burns, neonatal sepsis, and in the prevention of fibrosis after RT.[9,10]

In a randomized, controlled trial conducted by Jakobsen et al.[3], 53 patients with breast cancer were divided into two groups. One group received pentoxifylline 400 mg three times daily and vitamin E 400 IU perorally (n=26) at therapeutic doses. At the end of the treatment, the tissue thickness was measured, and the two groups were compared. The tissue thickness in the group that received therapy was significantly ($p=0.0478$) lower compared to that in the other group, and RT was better tolerated in this group.

Famoso et al.[11] demonstrated that administration of oral pentoxifylline 400 mg three times daily in 90 patients with breast cancer reduced fibrosis when used in combination with 400 IU single doses of vitamin E per day after RT for breast cancer.

The protective effect of pentoxifylline has been studied in an experimental study by Aygenç et al.[12] Sixteen adult New Zealand mice were divided into two groups: one group received pentoxifylline, and one group did not. After 30 weeks, changes in the skin and soft tissues caused by pentoxifylline were examined histopathologically. The group treated with pentoxifylline had little or no tissue damage, and the group that did not receive pentoxifylline had tissue damage. As a result, it was concluded that pentoxifylline had a protective effect.[12,13] In a clinical study conducted by the same investigator on 87 cases, pentoxifylline did not have any effects on the early period effects of radiation ($p>0.05$), whereas there was a significant difference between the late-period results ($p<0.05$).[14]

In a retrospective study examining the late-period effects of RT that are permanent and decrease the quality of life, 30 cases received pentoxifylline 400 mg three times daily for 8 weeks. The mechanism of action was examined by evaluating clinical and biochemical changes in these cases. The authors found that pentoxifylline decreased plasma cytokine levels, mainly TNF al-

pha and EGF2, in the case of fibrosis. In the same study, cases receiving RT following surgery were evaluated in two groups. Pentoxifylline group had significantly better skin results in the late period, and the effects on the outcomes in the early period were not significant. These data indicate that pentoxifylline is beneficial in terms of both improving the circulation in the irradiated area and showing activity against local changes through its systemic effects. The authors have reported that pentoxifylline might be recommended as prophylaxis.[15]

In our study, in Group A, 24 cases had a score of 0, 11 cases had a score of 1, seven cases had a score of 2, and two cases had a score of 3 in the early period. In the same group, 26 cases had a score of 0, 10 cases had a score of 1, five cases had a score of 2, and three cases had a score of 3 in the late period. In Group B, 20 cases had a score of 0, 10 cases had a score of 1, five cases had a score of 2, and three cases had a score of 3 in the early period. In Group B, 15 cases had a score of 0, 12 cases had a score of 1, six cases had a score of 2, and five cases had a score of 3 in the late period. In general, scores of 0, 1, and 2 are interpreted as cosmetically very good, good, and adequate, and a score of 3 is interpreted as poor in the clinical practice. Two (5%) cases in Group A and five (13%) cases in Group B had a score of 3, which represents a poor cosmetic outcome. The method used in our study to investigate the prophylactic effect of pentoxifylline is different from those reported in previous studies; however, the differences in early-period results between the two groups were not significant, whereas the differences in late-period results were significant (p=0.001). Our findings are comparable with those in the literature.

Owing to the fact that RT exhibits a late toxic effect in 10% of all cases, it is considered that pentoxifylline has a protective effect.[5,7,9] The results of the cases included in our study were evaluated using a scoring system based on physical examination. We have no tangible data on the systemic effect of the agent used, which represents a limitation of our study. However, no other studies have investigated the effect of pentoxifylline in patients with breast cancer who were treated with IOERT; this makes our study unique.

Furthermore, other agents have been studied for systemic radiation toxicity. One of these is curcumin, which has been evaluated in several studies.[16,17] In a double-blind study conducted on 30 cases who received curcumin 6 mg perorally per day, it was demonstrated that curcumin reduced radiation-induced fibrosis; however, it was noted that it should be used with caution due to some side effects, and further studies are needed regarding its routine use.[16] In another study, curcumin and placebo were administered orally as 500 mg capsules three times daily in 686 cases during the entire course of RT and the following 1 week. When compared with the placebo group, it was reported that it did not make a difference in terms of protection against late effects such as fibrosis, although it reduced symptoms such as pain and rigidity (p=0.082).[17] In this study, curcumin was administered at a lower dose and was better tolerated by the patients compared to those in other studies. However, it has been reported that the level of effect was not sufficient. In the literature, it has been reported that pentoxifylline had adverse effects on the digestive system; however, it has also been reported that these effects occur more frequently at therapeutic doses.[15] In our series, the patients were administered pentoxifylline 600 mg for prophylactic purposes, and no adverse effects were observed.

Some methods have also been attempted to reduce the effects of radiation locally. There are publications reporting that the hydrophilic cover is protective while delivering adjuvant RT. This method has spectrophotometrically demonstrated a decrease in skin changes such as erythema and peeling.[18]

Studies on the effects of radiation are usually related to the treatment of radiation-induced changes. There are limited studies on preventive agents or applications. Although the number of cases was low and the follow-up period was limited in our study, this study was different from other studies in that it searched for a preventive factor. In general, the methods that are used include personal hygiene and measures such as the use of clothing items and creams containing corticosteroids.[6,9] In addition, nonsteroidal creams, including zinc oxide, biafine, aluminum, sucralfate, and hyaluronidase-based creams, have been studied.[9] In this series, we opted for the local treatment with creams (zinc oxide and dexpanthenol) in cases that had a score of 3 despite pentoxifylline treatment (two cases in Group A and five cases in Group B).

Previous studies comparing scales for the evaluation of radiation-induced toxic effects have mostly focused on the importance of blood circulation and its measurement.[18] Pentoxifylline, which prevents the negative effects of RT by promoting blood circulation and oxygenation in the tissues, fits this definition.[9,13,15]

In the present study, we preferred pentoxifylline because it is systemically easy to use, has negligible side effects, and reduces the local effects of RT. We compared, examined, and shared the results of patients with breast cancer that used pentoxifylline for prophylactic purposes following IOERT and WBRT; to the best of our knowledge, this subject has not been studied in the literature yet.

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Conclusion

In the present study, patients who underwent BCS+IOERT and WBRT for breast cancer were categorized into two groups-A (receiving pentoxifylline) and B (not receiving pentoxifylline)-and they were presented and compared. Pentoxifylline has been shown as effective in protecting against radiation injury in cases undergoing RT as part of breast cancer treatment ($p<0.005$).

We conclude that the use of pentoxifylline in a prophylactic dose will contribute to cosmetic results and the quality of life.

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