Striking Regression of Chronic Radiotherapy Damage in a Clinical Trial of Combined Pentoxifylline and Tocopherol

By Sylvie Delanian, Saida Balla-Mekias, and Jean-Louis Lefaix

Purpose: **Radiation-induced fibrosis (RIF) remains the most morbid complication of radiotherapy because of the absence of spontaneous regression and the difficulty of patient management. RIF treatment with combined pentoxifylline (PTX) and tocopherol (Vit E) was prompted by recent advances in cellular and molecular biology that have improved researchers' understanding of radiation-induced late-injury mechanisms and by the excellent results from our previous human and animal studies.**

Patients and Methods: **Forty-three patients (mean [± SD] age, 59 ± 10 years) presenting with 50 symptomatic RIF areas involving the skin and underlying tissues were treated from April 1995 to September 1997. Patients had had radiotherapy for head and neck or breast cancer a mean period of 8.5 ± 6.5 years previously. RIF developed in the first year after irradiation and gradually worsened, without spontaneous regression. The mean measurable surface area of RIF ([S]) at the time of this study ($[S_0]$) was 42 ± 34 cm^2. The initial Subjective Objective Medical management and Analytic (SOMA) injury evaluation score was 13.2 ± 5.9 and included evidence of edema, plexitis, restricted movement, and local inflammatory signs. A combination of PTX (800 mg/d) and Vit E (1,000 IU/d) was administered orally for at least 6 months.**

Results: **Treatment was well tolerated. All assessable injuries exhibited continuous clinical regression and functional improvement. Mean RIF surface area and SOMA scores improved significantly ($P < .0001$) at 3 months ($[S_3]$, −39%; $[SOMA_3]$, −22%), 6 months ($[S_6]$, −53%; $[SOMA_6]$, −35%), and 12 months ($[S_{12}]$, −66%; $[SOMA_{12}]$, −48%), and mean linear dimensions ([D]) diminished from the start of the study ($[D_0]$, 6.5 ± 2.5 cm) to the end of treatment 12 months later ($[D_{12}]$, 4 ± 2 cm). At the time of the treatment, we did not attempt to achieve the maximum effect, and the study was continued.**

Conclusion: **The PTX-Vit E combination reversed human chronic radiotherapy damage and, because no other treatment is presently available for RIF, should be considered as a therapeutic measure.**

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THE APPLICATION OF radiation therapy to the treatment of malignant tumors is limited by the need to avoid excessive late damage to normal tissues. Although new strategies designed to improve the therapeutic ratio have reduced the incidence of severe radiation-induced fibrosis (RIF), RIF is still sometimes unavoidable and may cause severe handicaps in many patients. Several treatment-related factors have been indicated as causes of chronic radiotherapy damage, such as the total radiation dose, the dose per fraction, or the irradiated volume.[1,2] However, in most cases, the increased incidence and severity of fibrosis are due to factors connected with the patient's medical history, such as microvascular diseases, systemic sclerosis,[3] and especially concomitant chemotherapy or prior bloody surgery.[2] Despite these factors, slight differences exist in the clinical presentation of RIF.[4]

Constituted RIF does not regress spontaneously. Like fibrotic sequelae of any origin, RIF is primarily characterized by nonspecific changes in connective tissue, with excessive extracellular matrix deposition and the presence of an inflammatory infiltrate, consistent with an early, active RIF.[5,6] By contrast, an old, constituted RIF that develops with time from an early, active RIF presents a dense, noninflammatory fibrous matrix with fewer cells.[7,8] No efficient treatment for RIF has yet been established: RIF either stabilizes or gradually worsens, with acute inflammatory periods. Several categories of drugs seem to be potentially useful for managing all types of fibrotic sequelae, but they are only effective if they are administered prophylactically or in the early stages of fibrosis. These drugs include corticosteroids and nonsteroidal anti-inflammatory agents, hemorheologic and vasodilator drugs, zinc, and interferon.[2] Corticosteroids have proved useful in reducing the symptoms of acute inflammatory reaction associated with fibrosis, but they are relatively ineffective in reversing the fibrotic process. In our clinical and experimental experience, vasodilators have no effect on constituted RIF, probably because of the lack of reactivity in irradiated capillaries and the presence of arteriovenous shunts.[6] We recently showed that superficial RIF regressed after treatment with exogenous superoxide dismutase (SOD),[9,10] but this drug is not yet available.

From the Service d'Oncologie-Radiothérapie, Hôpital Saint-Louis, Paris; and the Laboratoire de Radiobiologie et d'Etude du Génome, Direction des Sciences du Vivant, Commissariat a l'Energie Atomique, Saclay, France.

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Address reprint requests to S. Delanian, MD, PhD, Service d'Oncologie-Radiothérapie, Hôpital Saint Louis, 1, Ave Claude Vellefaux, 75010 Paris, France; email delanian@chu-stlouis.fr.

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Despite the scant amount of information in the literature on the pathophysiologic mechanisms and management of chronic radiotherapy damage, we have tried to develop a treatment for RIF. For this, we considered that pentoxifylline (PTX) and alpha-tocopherol (Vit E) might be effective by interacting with the fibrotic process. Furthermore, it was shown that radiation-induced soft-tissue necrosis healed significantly faster with PTX treatment.[11,12] One case report mentioned that PTX relieved pain,[13] which was later confirmed in six patients with fibrosis.[12] In a preliminary PTX trial comprising eight patients with nonmeasurable RIF, functional improvement was reported by some of the patients, although there were three cases of poor tolerance.[14] Because SOD has proved effective in the treatment of RIF, partly because of its action as an antioxidant,[7] we believed that Vit E might also be of interest in this respect. In a preliminary study in which 700 IU/d of Vit E was administered to 53 patients, the mean linear regression of superficial RIF observed after 4 months was 20%.[15] However, when used separately, PTX and Vit E did not constitute a treatment for RIF. Consequently, we tested a combination of PTX and Vit E in a preliminary study of ten patients and observed 64% regression in the RIF surface area after 6 months of treatment.[16] We then decided to use our experimental model of cutaneomuscular RIF[10] in pigs given the PTX-Vit E combination and observed a regression of 70% in the volume of fibrotic tissue after 6 months of treatment.[17]

For the study presented here, 100 RIF patients from various institutions were evaluated between April 1995 and September 1997. We treated 43 of these patients (who, in all, had 50 assessable areas of symptomatic chronic radiotherapy damage) in a phase II clinical trial of combined PTX and Vit E therapy.

PATIENTS AND METHODS

As stated above, 43 patients presenting with 50 distinct zones of chronic radiotherapy damage were treated with combined PTX and Vit E. Informed consent was obtained from all patients before treatment started, and the study was approved by a French ethics review board. Thirty-eight patients (88%) were women. Patients' ages ranged from 37 to 82 years (mean ± SD, 59 ± 10 years). All patients had had radiotherapy for malignant tumors and showed no evidence of recurrent disease on entering onto the trial. RIF developed in the year after irradiation and gradually worsened. The mean latency period between the end of radiotherapy and the start of combined PTX-Vit E treatment was 8.5 ± 6.5 years (range, 0.5 to 30 years). In all of these selected patients, prior treatments, including corticosteroid therapy, had had no beneficial effect on RIF but had occasionally reduced acute inflammatory signs.

Radiation Damage

RIF had been caused by standard irradiation of 1.8 to 2.5 Gy per fraction, 4 to 5 days per week. Although the total doses prescribed ranged from 45 to 75 Gy, the total doses received locally sometimes exceeded 90 Gy. RIF correlated with excessive local radiation doses resulting from overlapping at field junctions, large brachytherapy or electron boost, low-voltage radiation therapy for deep tumors in corpulent patients, and personal sensitivity factors.

Forty-one of the 50 RIF areas were caused by adjuvant postoperative breast cancer radiotherapy, with chemotherapy involved in 91% of them. Seventeen RIF areas (42%) were located in regions that had been altered by previous local surgery with an interstitial brachytherapy boost, and 24 (58%) were outside surgically altered areas. Seven of the 34 breast cancer patients had developed RIF in two parts of the breast and at a field junction. Another seven RIF patients had had head and neck irradiation, and two others had had deep-seated tumors. Three types of RIF were evaluated: mammary-gland RIF (16 areas), superficial tissue on mammary-chain RIF caused by overlapping at field junctions (18 areas), and cervical, axillary, or inguinal body roots RIF (16 areas).

Treatment

The modalities of treatment were determined on the basis of pharmacokinetic data, clinical use in the treatment of other diseases, and long-term tolerance. Twice a day, each patient was given a combination of 400 mg PTX and 500 IU Vit E. This combination was continued for at least 6 months and after that for as long as clinical regression was observed. With regard to PTX, our choice of combined PTX-Vit E dosages was designed to avoid severe adverse effects in patients without vascular disease and, with respect to Vit E, to supply sufficient antioxidant activity.

Study Assessments

Patients underwent separate assessments by two physicians. Routine evaluations included palpation of the edges of the fibrotic block and measurement of the length and width of the projected cutaneous surface in the maximum possible number of the 41 palpable and measurable RIF areas of the 50 that were assessable (82%). One year before treatment, clinical assessments of each patient had shown that each case of RIF was stable. The mean initial linear dimension ($[D_0]$) of fibrosis ([length + width]/2) was 6.5 ± 2.5 cm, and the projected cutaneous surface area (length × width) was 42 ± 34 cm^2.

Objective signs and subjective symptoms relating to the site of fibrotic involvement were graded from 1 to 4 according to the Subjective Objective Medical management and Analytic evaluation of injury (SOMA) system[18]; the items assessed included scaliness, pruritus or pain, local edema, pigmentation changes, ulcer or necrosis, telangiectasia, fibrotic scarring, atrophy or tissue contraction, and medical management of local pain or compressive edema. All patients exhibited areas of RIF involving the skin, subcutaneous tissues, and, occasionally, the underlying skeletal muscle and bone. Patients complained of various local signs such as telangiectasia (21 areas); tumor, erythema, hardness, skin retraction, and local pain (24 areas); and soft tissue necrosis inside the fibrosis (two areas). Clinical evidence of local inflammation was observed in 12 (24%) of 50 RIF areas. Sixteen patients with chronic RIF had associated symptoms in the extremities, including restricted arm, leg, or neck movement in nine patients; severe limb edema in eight; and sensorimotor nerve dysfunction with symptomatic plexitis lasting longer than 2 years in six.

The mean initial SOMA score ($[SOMA_0]$) was 13.2 ± 5.9 and was significantly affected by the RIF latency period ($P < .0001$), RIF topography (body roots *v* breast/mammary chain: 19 ± 6 *v* 11 ± 3, respectively; $P < .0001$), and local inflammatory signs (inflammatory *v* noninflammatory constituted RIF: 16.1 *v* 12.3, respectively; $P = .04$), but not by age or local pain.

The results of the treatment were evaluated at 3, 6, and 12 months (T_3, T_6, and T_{12}, respectively) by measuring the percentage changes in the linear dimensions (D_x), surface area (S_x), and the SOMA score ($SOMA_x$); the patients were used as their own controls (paired data).

Statistical Analysis

Depending on the quantitative or qualitative assessments, data were analyzed using Statview software (Statview IV; Abacus Concepts, Berkeley, CA) and compared by a paired Student's *t* test or the chi-square test for hypothesized correlations. A P value of $< .05$ was considered to be statistically significant. The data for surface regression at 6 months and the SOMA score were processed by single-sample tests and bivariate plots.

RESULTS

Adverse Events

Immediate and long-term tolerance were very satisfactory. Two patients with one RIF area each stopped their treatment after 3 months because another, different disease occurred and were not evaluated thereafter. Two others did not tolerate PTX because of severe asthenia and vertigo and stopped only the PTX treatment after 3 months. However, these two patients were included in the final evaluation because they experienced a rapid, major RIF regression in the first 3 weeks of combined PTX-Vit E treatment and because this response stabilized when treatment was continued with Vit E alone. Two other patients experienced discomfort during the first 3 weeks because of mild nausea and dyspepsia but remained on the study with a daily dose of PTX reduced from 800 to 400 mg.

Quantitative Changes

Clinical regression was observed in all of the 41 palpable areas of the 50 assessable RIF zones. This response was a centripetal reduction of the edges of the fibrotic block without RIF contraction or atrophy. The mean 53% regression of RIF surface areas at 6 months (T_6) was highly significant ($P < .0001$), and the mean linear dimensions diminished from [D_0] 6.5 cm to [D_6] 4.5 cm (Table 1). The responses in fibrotic zones were classified into four types of response, according to the percentage of RIF surface area regression at T_6 (n = 40): two areas, no response (0% to 24%); 14 areas, slight response (25% to 49%); 18 areas, moderate response (50% to 74%); and six areas, excellent response (75% to 100%), with complete regression in three RIF areas. An objective response (more than 50% of RIF surface regression) was observed for ten of 41 RIF areas (24%) at T_3, 24 (60%) of 40 RIF areas at T_6, and 23 (83%) of 28 RIF areas at T_{12} (Fig 1). These delayed responses to combined PTX-Vit E treatment emphasized a continuous slow efficacy even after 12 months.

Table 1. Quantitative Changes in 41 Measurable Palpable Areas of the 50 Assessable Cases of Chronic R Induced Fibrosis After Combined Treatment With PTX and Vit E

	Time (no. of RIF cases assessed)			
	T_0 (n = 41)	T_3 (n = 41)	T_6 (n = 40)	T_{12} (n = 28)
D ± SD, cm	6.5 ± 2.5	5 ± 2.5	4.5 ± 2	4 ± 2
Percent D changes (± SD)		−22 ± 14	−33 ± 17	−41 ± 18
S ± SD, cm^2	42 ± 34	27 ± 26	19 ± 18	17 ± 18
Percent S changes (±SD)		−39 ± 18	−53 ± 20	−66 ± 16
P		.0001	.0001	.0001

Qualitative Changes

All 50 assessable RIF areas responded to treatment well, and at 6 months, symptom severity had diminished by half (Table 2). Responses were graded qualitatively according to the SOMA system. Mean SOMA scores improved significantly (Fig 2), from 13.2 at T_0 to 6.9 at T_{12}. Although the assessable qualitative SOMA changes correlated with the measurable quantitative changes in RIF surface area ($P < .0001$), a poor early response was not indicative of the extent and quality of the delayed maximum response.

All RIF areas improved rapidly with regard to local pain, and 23 of 24 patients no longer required analgesic drugs at T_6. All areas exhibited slight to excellent evident softening of the tissues without RIF contraction or skin atrophy during treatment. Fibrotic adhesions to overlying skin or underlying bones regressed so that the palpated residual fibrotic zone could be freely moved in relation to these structures. In cases of cutaneous or dermis atrophy that had been present before treatment, slight modifications of these conditions were noted. However, telangiectases were difficult to assess: at T_6, their number and intensity of color were stable or had been reduced by 20%. Also at T_6, the local inflammatory signs initially observed in 12 RIF areas had completely disappeared in ten areas (83%) and were greatly reduced in the two others. At T_{12}, no residual inflammatory signs were observed. There was no difference between the quality of the response to treatment by noninflammatory constituted RIF and inflammatory RIF. The two cases of severe skin ulceration with deep subcutaneous necrosis in a large RIF area, which persisted for longer than 6 months without spontaneous healing, exhibited superficial healing at T_3.

Patients with restricted shoulder or neck movements experienced a marked functional improvement of 10° to 20° every 3 months. Although the progression of neurologic disturbances was arrested, no measurable improvements in this respect were observed at T_6, and only one case of such disturbances had improved at T_{12}. Lastly, patients who had

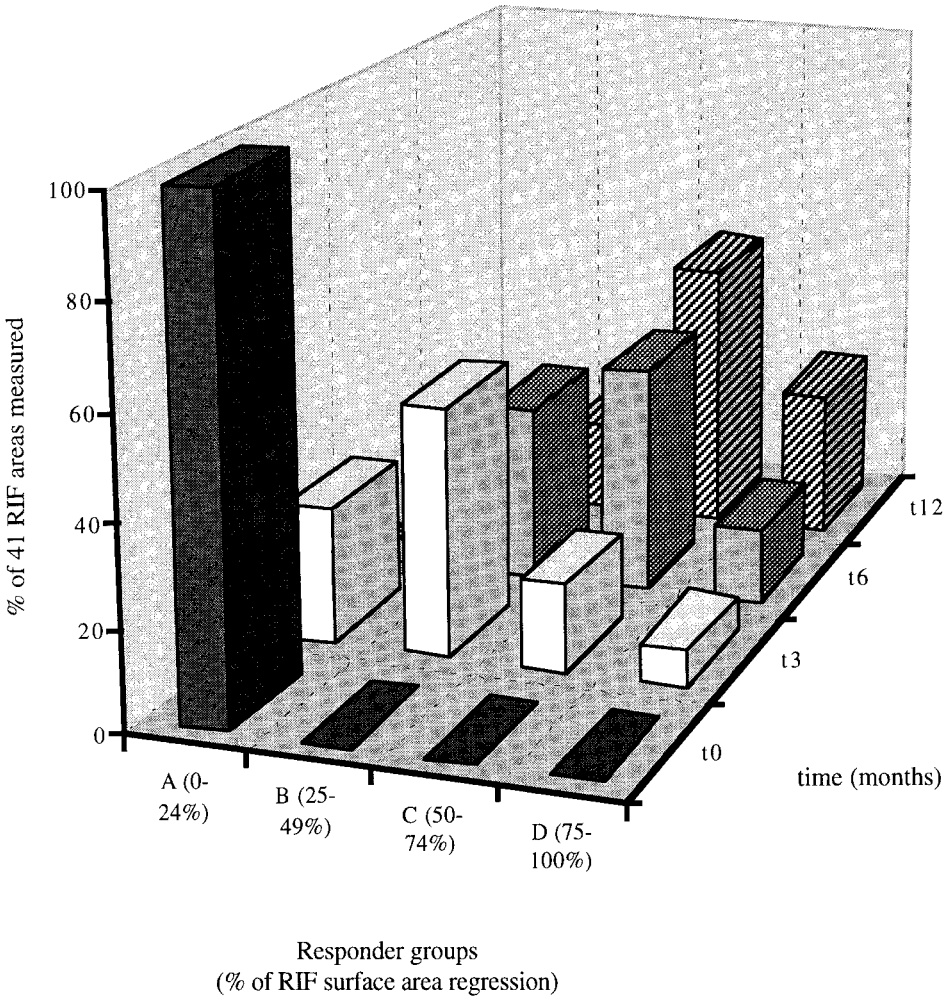

Fig 1. Time to quantitative response in 41 measurable areas of RIF after combined PTX-Vit E treatment. The curve for the percentage of RIF surface regression formed a wave, moving from the group of poor responders at 3 months to the group of objective responders at 6 and then 12 months.

experienced an evolutive attack of severe facial or limb edema every month only had such attacks every 3 months at most after 6 months of treatment (Fig 3).

Pathologic Subtypes

At T_6, we did not find any significant interaction between treatment effect and the following covariates (Table 3): age, RIF latency period, [S_0], [$SOMA_0$], RIF topography, and inflammatory signs. We found two dissociated responses: larger surface regression in recent cases of RIF (< 6 years) and a larger SOMA score regression for patients with painful RIF. The seven patients with two RIF zones, each of which had occurred after breast cancer treatment, displayed a proportional mean decrease in both zones (Fig 4).

Table 2. Qualitative Changes in 50 Assessable Cases of Chronic RIF After Combined Treatment With PTX and Vit E

	Time (no. of RIF cases assessed)			
	T_0 (n = 50)	T_3 (n = 50)	T_6 (n = 48)	T_{12} (n = 32)
SOMA ± SD	13.2 ± 5.9	10.2 ± 4.8	8.6 ± 5.0	6.9 ± 4.8
Percent SOMA changes ± SD		−22 ± 14	−35 ± 20	−48 ± 21
P		.0001	.0001	.0001

DISCUSSION

Recent Advances in Understanding Chronic Radiotherapy Damage

The clinical and histologic descriptions of late radiation damage to normal tissue date back to the first decade of the therapeutic use of ionizing radiation,[5] but it is only recently that the advances in cellular and molecular biology have significantly helped to clarify the nature of the mechanisms that cause late injury.[7,8,19,20] The production of free radicals caused by the interaction of ionizing radiation with living tissues plays an important role in the initial biologic damage and the ensuing inflammatory response until fibrosis occurs, which appears to be the results of a continuous, self-maintaining local process. The presence of heterogeneous

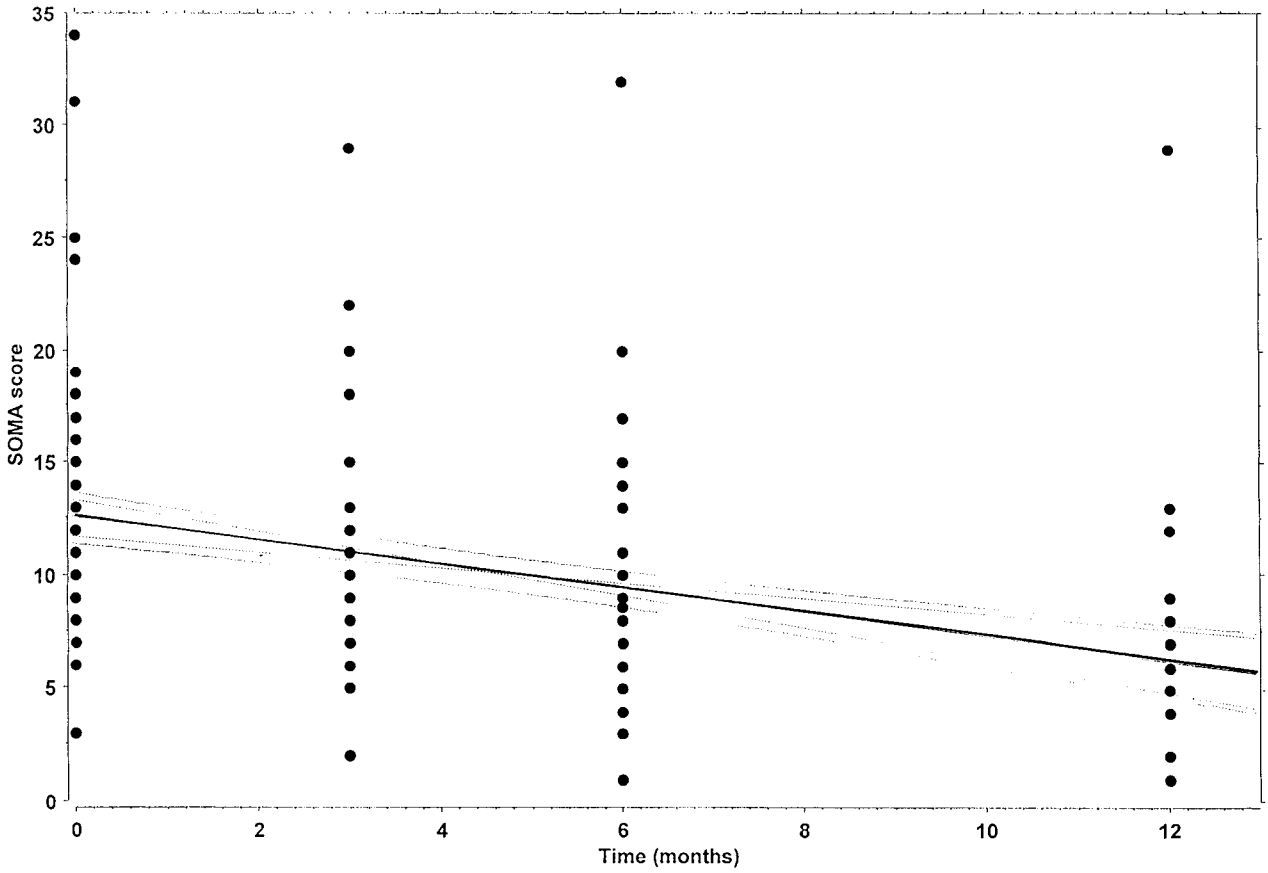

Fig 2. Time to qualitative response in 50 assessable areas of RIF after combined PTX-Vit E treatment. The linear regression of response at 3, 6, and 12 months was highly significant ($P < .0001$) and SOMA scores formed the curve shown below (score = 12.4 − 0.525 × time). ——, SOMA scores curve; – – –, standard deviations.

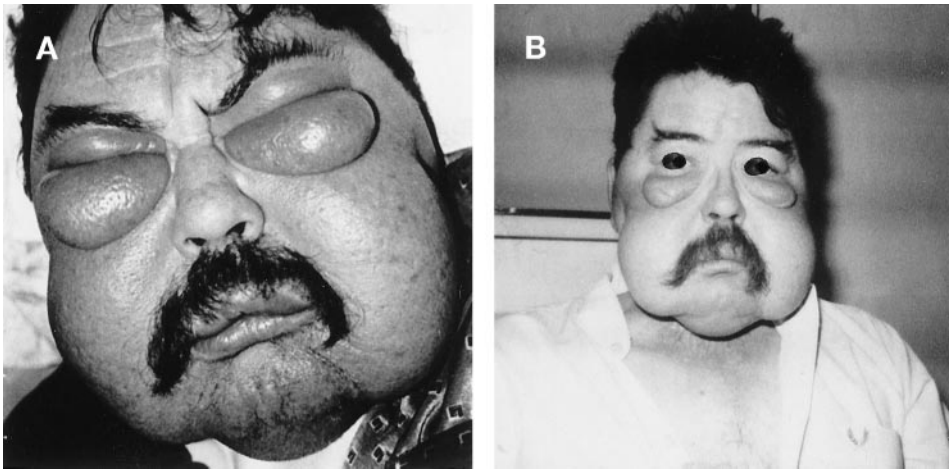

Fig 3. This man had undergone total laryngectomy followed by 60 Gy radiation therapy in 1992. (A) In 1995, he presented with a small cervical skin ulcer, incapacitating facial edema, and dyspnea (SOMA score, 31). (B) Six months after combined PTX-Vit E treatment, the ulceration had healed, the edema had regressed, and the dyspnea had ceased (SOMA score, 28).

Table 3. Quantitative Surface Area Regression and Qualitative SOMA Score Percentage Regression in 50 Assessable Cases of Chronic RIF After 6 Months of Combined Treatment With PTX and Vit E: Interaction Between Several Covariates and Treatment Effect

Variable	No.	Percent Surface Change	*P*	Percent SOMA Change	*P*
Patient age, years					
< 60	26	−48 ± 20	NS	−33 ± 21	NS
≥ 60	24	−57 ± 21		−37 ± 18	
RIF latency period, years					
≤ 6	21	−62 ± 22	< .0001	−35 ± 23	NS
> 6	27	−45 ± 15		−34 ± 17	
Local RIF inflammatory signs					
Inflammatory	12	−49 ± 25	NS	−30 ± 22	NS
Noninflammatory	38	−54 ± 19		−36 ± 19	
Pain					
Yes	24	−51 ± 23	NS	−41 ± 23	.04
No	26	−55 ± 17		−29 ± 15	
RIF topography					
Breast and mammary chain	34	−52 ± 22	NS	−37 ± 21	NS
Body roots	16	−57 ± 11		−29 ± 16	
Initial SOMA score					
< 10	16	−45 ± 19	NS	−32 ± 21	NS
≥ 10	24	−57 ± 20	(.07)	−36 ± 19	

cell populations was recently shown in tissue with chronic radiotherapy damage that contained myofibroblast-like proliferating cells and senescent nonproliferating cells,[7,21] probably because of a variable balance between reactive oxygen species and the antioxidant defense system.[22] The same cellular pattern was found in our previous histopathologic examinations of porcine RIF tissues, whose appearance greatly varied in the same tissue biopsy[6,23]: thus areas containing myofibroblasts, inflammatory cells, and interlaced fibers coexisted with stromal areas containing scattered fibroblasts. Whereas senescent irradiated tissue was primarily characterized by exhausted cells, early RIF tissues were found to be more active, displaying excess myofibroblastic proliferation, increased production of transforming growth factor beta 1 (TGF-β1), and increased synthesis and deposition of extracellular matrix components, amplified by activated cells in endothelial and connective tissues.[19,24-27] In fact, from a clinical point of view, chronic radiotherapy damage may also combine atrophy/contraction and conjunctive hypertrophy/fibrosis in the same damaged area, with specific symptoms including subcutaneous fibrosis, soft-tissue necrosis, radiation pneumonitis, rib fracture, ''frozen'' shoulder, pericarditis, or breast contraction. Here we found that, as expected, the SOMA scoring system (which was the result of international cooperation) improved data recording at regular intervals and provided a standardized system for categorizing these late toxic effects.[18]

Clinical Efficacy of the PTX-Vit E Combination

The significant reduction in all chronic radiotherapy damage with use of the PTX-Vit E combination does not support the concept that established sequelae such as fibrosis are irreversible. In the series presented here, an objective response to treatment at 12 months was recorded in 23 (83%) of 28 RIF areas, with a mean decrease of two thirds in their surface areas and of half in their SOMA scores. These results confirmed our previous experimental data for the histopathologic normalization of the subcutaneous tissues surrounding the residual scar in PTX-Vit E–treated pigs, as well as the large reduction in TGF-β1 expression.[17] The results presented here are highly significant when taken

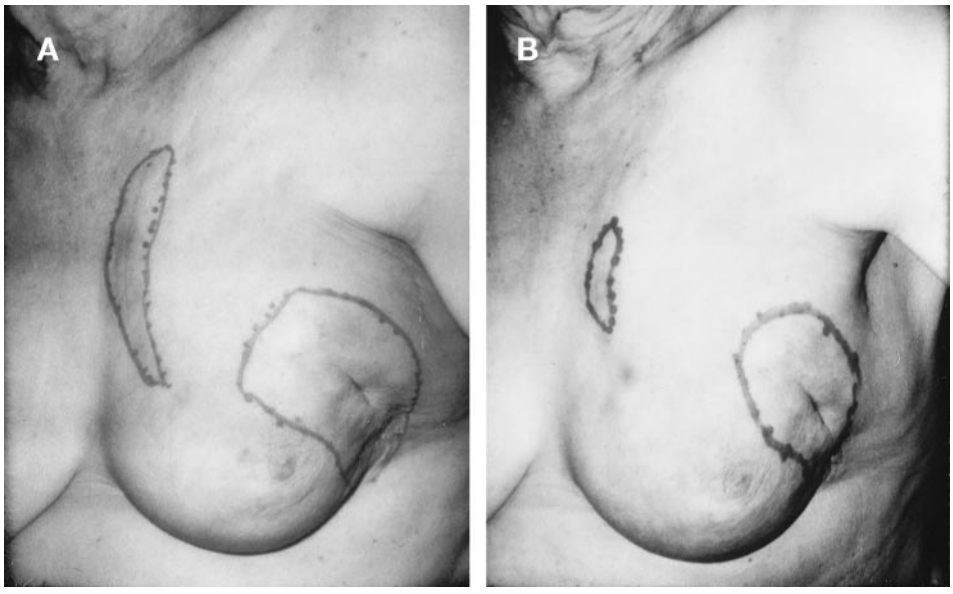

Fig 4. In 1981, this woman underwent breast surgery followed by 20 Gy brachytherapy and 45 Gy radiation therapy. (A) In 1996, she had 12 × 7 cm breast fibrosis (SOMA score, 12) and 11 × 3 cm internal mammary chain fibrosis (SOMA score, 12). (B) Twelve months after combined PTX-Vit E treatment, the fibrosis surface regression was 44% for the breast (SOMA score, 8) and 82% for the mammary chain (SOMA score, 5).

together with the stability observed in the PTX-treated and control animals. Moreover, as far as we know, the PTX-Vit E combination has provided the best results ever published in the literature for measurable RIF in humans. Although the regression of 53% obtained here at T_6 was similar to the regression of 57% that we previously obtained in patients treated for 2 months with SOD,[9] the 66% regression obtained in this trial at T_{12} with combined PTX-Vit E has never been reported. In addition, the response by patients with various etiopathogenic subtypes of RIF was equivalent whether these patients had initially been treated by radiation alone or had also had surgery and/or chemotherapy, a result not observed in the SOD study.[9]

Biological Bases of the PTX-Vit E Combination

The precise mechanisms by which the PTX-Vit E combination interacts with fibrotic tissues are not yet known. However, several items of biologic information suggest some reasons why this combination has proved useful. PTX is a methylxanthine derivative used to treat vascular diseases such as intermittent claudication. In vivo, it has been reported to increase erythrocyte flexibility, to vasodilate, and to inhibit inflammatory reactions and tumor necrosis factor. Many in vitro studies have indicated that PTX inhibits human dermal fibroblast proliferation and extracellular matrix production[28,29] and increases collagenase activity.[30,31] However, in our experimental pig study, we observed no clinical or histologic changes in RIF after 6 months of treatment with PTX alone.[17] The high concentration of PTX necessary to suppress fibroblast collagen synthesis or to increase collagenase activity, as deduced by extrapolation of the results of in vitro studies, suggests that administration of PTX alone does not constitute an antifibrotic treatment. The physiologic role of Vit E, used in clinical practice to lower cholesterol levels, is to scavenge the reactive oxygen species generated during oxidative stress when their production is not limited by antioxidant enzymes such as SOD or catalase and to protect cell membranes against lipid peroxidation. Fifty years ago, it was observed in humans that endogenous Vit E deficiency was associated with abnormal connective tissue repair, resulting in the formation of scar-like tissues. Benritter et al[32] showed in vivo that endogenous Vit E was significantly consumed in irradiated rat heart tissue. In vitro, we showed reduced endogenous Mn SOD and catalase activities in surviving cell cultures from human tissue with chronic radiotherapy damage.[7] In a mouse model of hypersensitivity pneumonitis generated by actinomycetes and treated with several antioxidants, only Vit E and SOD significantly reduced the development of lung fibrosis.[33] In carbon tetrachloride–induced rat liver fibrosis, long-term Vit E supplementation inhibited the expression of TGF-β1 and the procollagen gene.[34] Until now, PTX or Vit E alone have not been able to reverse the development of fibrosis. Nevertheless, they have all of the major properties necessary to make them excellent antifibrotic agents. This is why we explored the action of two different but complementary mechanisms whose effect is not simply additive. Combined PTX-Vit E treatment may exert synergistic action on both the extracellular matrix and cell regulation. The combination's beneficial effects observed in the study presented here, on both hypertrophic fibrotic and contracted areas as reflected by SOMA scores, and in our previous experimental study, on the disappearance of fibrotic tissue with replacement by normal subcutaneous and skeletal muscle tissues around the residual scar,[17] suggest that great changes take place during treatment in the genetic programming of the cell differentiation that characterizes RIF. We postulate that the target of the PTX-Vit E combination could be in vivo reversal of the abnormal phenotype of RIF fibroblasts. This hypothesis was supported by the disappearance of the overexpression of TGF-β1, the key cytokine in RIF tissues,[17] after combined PTX-Vit E treatment.

In conclusion, the PTX-Vit E combination proved effective in reversing chronic radiotherapy damage in patients, and because there is presently no alternative treatment, we believe that it can constitute a reference treatment. Both drugs are available, well-tolerated, inexpensive, and socially beneficial because they reduce physical disabilities. The results of this trial raise many questions, primarily about the precise mechanisms of action of the drugs used. Some of the answers may be provided by the results of our ongoing cellular and molecular studies and randomized clinical trial. The striking results of the study presented here prompted us to propose the PTX-Vit E combination as the leading treatment in antifibrotic therapy.

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