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Pentoxifylline and vitamin E treatment for prevention of radiation-induced side-effects in women with breast cancer: A phase two, double-blind, placebo-controlled randomised clinical trial (Ptx-5)

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ABSTRACT

Background: A previous study has shown that pentoxifylline in combination with vitamin E can reverse radiation-induced fibrosis. The aim of the present study is to investigate if the same drugs could prevent radiation-induced side-effects in women with breast cancer.
Patients and methods: A randomised, placebo-controlled, double-blind, parallel group trial was performed. Women with breast cancer were treated for 12 months with 400 mg pentoxifylline t.i.d. or placebo, in combination with 100 mg vitamin E t.i.d., starting 1–3 months after the completion of radiotherapy. The primary end-point was passive abduction of the shoulder, and the secondary end-point was difference in arm volumes. The trial is registered on the ISRCTN.org website, number ISRCTN39143623.
Results: 83 patients were included in the study; 42 in the pentoxifylline + vitamin E group and 41 in the placebo + vitamin E group. Both treatments were generally well tolerated. Seven patients were withdrawn from the treatment due to disease progression; four in the pentoxifylline group and three in the placebo group. At inclusion, patients had impaired passive abduction of the shoulder. During treatment, both the groups improved significantly. Median improvement from baseline was 3.7° ($p = 0.0035$) on pentoxifylline and was 9.4° ($p = 0.0041$) in the placebo group, but no difference between the groups was detected ($p = 0.20$). Arm volumes increased over time in the placebo group (1.04%), but not on pentoxifylline (0.50%), and differed significantly between the groups ($p = 0.0172$).
Conclusions: The combination of pentoxifylline and vitamin E was safe and may be used for the prevention of some radiation-induced side-effects.

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1. Introduction

Breast cancer is one of the most common malignancies in women. In Sweden alone, 7059 new cases were diagnosed in 2006, with an incidence of 154 cases per 100,000 women.[1] The primary treatment is surgical resection of the tumour through breast conserving surgery or mastectomy, which is effective for the vast majority of women with early breast cancer. To improve cancer control and survival, women are treated with chemotherapy, hormonal therapy and radiotherapy based on the patient and tumour characteristics such as stage, tumour grade and hormonal receptor status. Radiotherapy reduces locoregional tumour recurrence within the irradiated area and prolongs survival,[2] but long-term side-effects of the radiotherapy often develop. Known late radiation side-effects are fibrosis of irradiated tissue and arm lymphoedema, severely influencing patient quality of life.[3,4] Factors associated with a higher risk of radiation-induced side-effects are treatment with both surgery and chemotherapy, large radiation-treated volumes, high total absorbed dose, radiotherapy to the axilla, coincident infection or complications from surgery.[5] In a recent review of 32 studies of side-effects of surgery and radiation on early breast cancer, Lee and co-workers showed that shoulder restriction was reported in 1–67% of patients and lymphoedema was reported in 0–34% of participants.[6]

Previously, radiation-induced fibrosis (RIF) was considered irreversible. However, Delanian and colleagues have shown that co-administration of pentoxifylline and vitamin E reduces the mean area of RIF up to 60% in women previously treated with radiotherapy for breast cancer in a double-blind, placebo-controlled study.[7] Pentoxifylline is a methylxanthine derivative used to treat conditions involving impaired regional microcirculation, such as peripheral vascular disease.[8–10] In addition, *in vitro* studies have indicated that pentoxifylline inhibits human dermal fibroblast proliferation and extracellular matrix production and increases collagenase activity.[11,12]

Reactive oxygen species are generated during inflammatory reactions and in the development of RIF.[13] Vitamin E has antioxidant properties, and may, therefore, be effective against the development of RIF, but no studies on prophylactic treatment were registered when planning this study. To determine the preventative effects of pentoxifylline and vitamin E against a range of radiation-induced side-effects, we performed a randomised, double-blind, placebo-controlled clinical trial for pentoxifylline. This study used women with breast cancer treated with surgery followed by radiotherapy, where all participants received a standard treatment with vitamin E.

2. Patients and methods

2.1. Study design

The study was a randomised, placebo-controlled, double-blind clinical trial for pentoxifylline with a parallel study design. Randomisation was stratified for previous use of chemotherapy. The study was conducted at Lund University Hospital, Department of Oncology, in accordance with the principles of Good Clinical Practice (GCP) and the ethical principles stated in the current revision of the declaration of Helsinki. The study was approved by the Ethics Committee of Lund University and by the Swedish Medical Products Agency. The trial is registered on the ISRCTN.org website, number ISRCTN39143623.

2.2. Patients

Inclusion criteria were primary breast cancer, mastectomy or segmental resection, axillary dissection of levels one and two, and radiotherapy to the breast/thoracic wall, axilla and fossae supra/infra clavicularis. The inclusion period was one to three months after termination of radiotherapy. Other active cancer treatment had to be completed at inclusion; however, endocrine treatment with tamoxifen, letrozol, anastrozole and exemestane was allowed as concomitant medication. Exclusion criteria were known sensitivity to pentoxifylline or vitamin E, disorders related to muscles or joints and/or treatment with corticosteroids during the radiotherapy treatment.

2.3. Radiotherapy

All patients had CT-based three-dimensional treatment planning. International recommendations of volume and dose definitions (ICRU) for clinical target volume (CTV), planning target volume (PTV) and organs at risk were followed. The PTV for locoregional treatment included the thoracic wall/breast tissue, supra and infra clavicular fossa, and levels II and III of the axilla. The PTV was treated to a total absorbed dose of 50 Gy given in 2 Gy fractions 5 days per week.

2.4. Treatments

After written informed consent and baseline assessments were obtained, patients were randomly assigned on a 1:1 basis, with stratification for chemotherapy, to pentoxifylline 400 mg 3 times daily or a matching placebo. All patients were treated with 100 mg vitamin E 3 times daily. The pentoxifylline/placebo doses were escalated. The initial dose was 400 mg once daily for two weeks, then 400 mg two times daily for two weeks and finally 400 mg three times daily for the remaining study period. The target dose was 400 mg three times daily and the total treatment time was 12 months for all patients. If this dose was not tolerated, the patient received the maximum tolerated dose.

2.5. Assessments

Prior to enrollment in the study, all patients underwent a physical examination and their medical history was taken. At inclusion, patients' demographics, breast cancer status and treatment history were assessed. At inclusion, and after 3, 6, 9 and 12 months of treatment, patients visited the clinic for the assessment of safety and compliance, measurement of end-points, and blood sampling.

2.6. Safety assessment

Patients were assessed for breast cancer recurrence and survival as a measurement of drug safety. At each visit, patients were asked if they had experienced any change in health status. Adverse events and serious adverse events were classified and reported based on the ICH GCP guidelines.

2.7. Efficacy assessment

The end-points consisted of changes in the passive abduction of the shoulder, changes in arm volume, Late Effects on Normal Tissue; Subjective, Objective, Management and Analytic, breast score (LENT-SOMA) as assessed by the patients' physicians,[14] and patients' subjective assessment of somatic sensations and discomfort during the last week as measured by the Visual Analogue Scale (VAS).[15] With the patient in a supine position, passive abduction of the shoulder was measured using a goniometer as recommended by the American Academy of Orthopaedic Surgeons. Arm volume was measured submerging each arm in water and measuring the displacement volume.[16,17] The unaffected arm was used as a reference at each measurement.

$$\frac{\text{Volume of the affected arm} - \text{volume of the unaffected arm}}{\text{Volume of the unaffected arm}} \times 100$$

A correction for the natural asymmetry of the arms was performed with 1.6% for right handed and 1.4% for left handed.

Blood samples were collected by venipuncture into vacuum collection tubes containing sodium heparin. Plasma concentrations of pentoxifylline and its major metabolites: 3,7-dimethyl-1(5′hydroxyhexyl)xanthine (R-M1 and S-M1), were determined by high-performance liquid chromatography as previously described.[18]

Patients were asked about their medication compliance and the number of unused tablets of study medication was

Table 1 – Baseline characteristics, counts or median (Q1–Q3), of all 83 patients.

	Pentoxifylline + Vitamin E N = 42	Placebo + Vitamin E N = 41
Patient		
Age (y)	56 (48–60)	57 (46–65)
Weight (kg)	69 (63–74)	72 (66–77)
Height (cm)	166 (163–169)	167 (164–171)
Smokers (n)	7	6
Blood pressure (mmHg)	128 (119–139)/83 (76–88)	130 (120–150)/85 (80–95)
Pulse (bpm)	72 (66–80)	74 (64–80)
Treatment		
Segmental resection (n)	9	8
Mastectomy (n)	33	33
Axillary dissection		
Total number of lymph nodes (n)	16 (13–19)	18 (13–22)
Normal lymph nodes (n)	9 (6–14)	7 (4–12)
Pathological lymph nodes (n)	6 (3–10)	7 (4–13)
pT1 (n)	15	12
pT2 (n)	16	17
pT3 (n)	2	2
pT4 (n)	0	0
ypT0 (n)	1	0
ypT1 (n)	5	3
ypT2 (n)	1	3
ypT3 (n)	0	3
ypT4 (n)	0	0
Unclassified (n)	2	1
pN0 (n)	1	0
pN1 (n)	5	2
pN2 (n)	16	17
pN3 (n)	11	12
ypN0 (n)	2	2
ypN1 (n)	3	0
ypN2 (n)	1	4
ypN3 (n)	1	3
Unclassified (n)	2	1
Patients treated with chemotherapy (n)	33	34
Patients treated without chemotherapy(n)	9	7

counted. Patients with at least 75% compliance were included in the per protocol (PP) analysis.

Patients were withdrawn from the study medication if the cancer recurred or if another life threatening disease occurred. Withdrawn patients were asked to come to the remaining visits in order to perform effect measurements.

2.8. Statistical methods

Continuous variables are presented as medians and quartiles. Categorical variables are presented as frequencies. Abduction, percentage difference in arm volumes, LENT-SOMA score and VAS observations were regarded as ordinal data. A two-way method was developed for repeated measures of ordinal scale data[19] using SAS statistical software version 8.2 (SAS, Cary, NC, USA) to elucidate differences between treatment over time and the time by treatment interaction in the effect data. Statistical significance was defined as two tail $p < 0.05$.

3. Results

Between May 2004 and May 2007, 83 patients were included in the study; 42 patients were randomised to pentoxifylline treatment and 41 to the placebo group. Most patients (67) had previously received chemotherapy; 33 in the pentoxifylline + vitamin E group and 34 in the placebo + vitamin E group. The baseline characteristics of the included patients are listed in Table 1. All 83 patients are included in the safety analysis and the intention to treat (ITT) efficacy analysis after 12 months of treatment (Fig. 1). Similar baseline characteristics as well as outcomes were found for the 75 patients with at least 75% medication compliance, comprising the per protocol population (PP). We report only the results from the ITT analyses.

3.1. Safety

Both treatments were generally well tolerated. Only four patients discontinued due to adverse events: two due to nausea and one due to bruising in the pentoxifylline group and one due to neuropathic pain in the placebo group. Two patients in the placebo group and one in the pentoxifylline group had their doses reduced due to side-effects. Six patients experienced serious adverse events: dizziness due to benign postural vertigo (NY08), transient ischemic attack (NY03), vaginal bleeding (HG12), hip fracture (MS99), pancreatitis (GI26), and seizures due to brain metastases (NY24). None of these events were considered related to treatment by the patients' physicians. Adverse events that were considered related to the treatment by the patients' physicians are listed in Table 2.

Seven patients were withdrawn due to disease progression during the treatment period; four in the pentoxifylline group and three in the placebo group. A safety analysis was done in September 2008 when all patients had been included in the study for a median period of 31 months (range 16–52 months). At that point, 19 patients had experienced disease progression, 10 in the pentoxifylline group and 9 in the placebo group; 8 patients had died, 5 in the pentoxifylline group and 3 in the placebo group.

3.2. Abduction

The median value for passive abduction at inclusion was 121° in the pentoxifylline group and was 117° in the placebo group

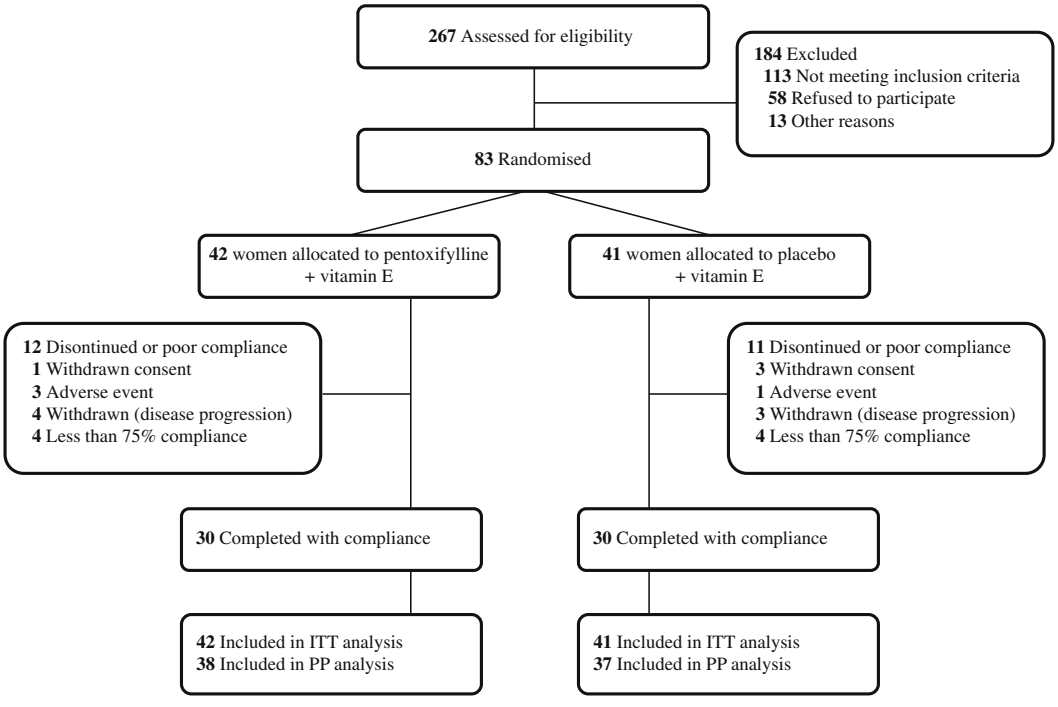

Fig. 1 – Study profile.

Table 2 – Number of patients with adverse events possibly or probably related to study medication, as determined by the patients' physicians.

	Pentoxifylline +Vitamin E	Placebo +Vitamin E
Endocrine		
Thyreotoxicosis	0	1
Eyes		
Bleeding conjunctiva	1	0
Gastrointestinal disorders		
Gastritis	1	0
Nausea	16	3
Vomiting	1	2
Diarrhoea	2	0
Gastrointestinal upset	1	1
General disorders		
Depression	0	1
Dizziness	1	2
Tiredness	6	0
Insomnia	1	0
Investigations		
Weight loss	1	0
Nervous system disorders		
Headache	1	0
Pain	1	1
Neuropathic pain	0	1
Skin and subcutaneous disorders		
Bruising	1	0
Sweating increase	1	0

(Fig. 2). Only seven of the 83 patients had maximal, obtainable passive abduction of the shoulder (180°). Both treatment groups improved in passive abduction during the 12 months treatment period. Median improvement in the pentoxifylline group was 3.7° ($p = 0.0035$) and that in the placebo group was 9.4° ($p = 0.0041$). These changes were not significantly different between treatments ($p = 0.20$).

3.3. *Volume*

At study start, there was no significant median difference in arm volume between the patients' affected and unaffected arms (Fig. 3). Six patients in each group had consistently more than 5% greater volume of the affected arm compared with the unaffected arm (i.e. volume criterion for lymphoedema); 1/34 patients in the pentoxifylline group and 2/33 patients in the placebo group had an increase of more than 5% during treatment. During the study, a difference between the treatment groups gradually developed. At the end of the treatment period, the median increase was 1.04% in the placebo group and was 0.50% in the pentoxifylline group, and was significant between groups ($p = 0.0172$).

3.4. *LENT-SOMA*

No significant differences were found at any time point between the treatment groups in LENT-SOMA total score or the sub-score of objective fibrosis. In the LENT-SOMA subscore for subjective pain, a significant decrease over time was documented in the placebo group ($p = 0.0022$), but not in the pentoxifylline group ($p = 0.35$). The LENT-SOMA subscore for management pain increased over time in the pentoxifylline group but not in the placebo group, and a significant difference between the groups was detected at 12 months ($p = 0.0248$).

3.5. *VAS*

No significant difference in VAS for subjective pain was (arm pain, local axillary pain or breast pain) detected at any occasion between the treatment groups. The VAS score for pain described as stiffness in the skin significantly decreased in the pentoxifylline group during the treatment time ($p = 0.0001$), but not in the placebo group ($p = 0.77$), Fig. 4.

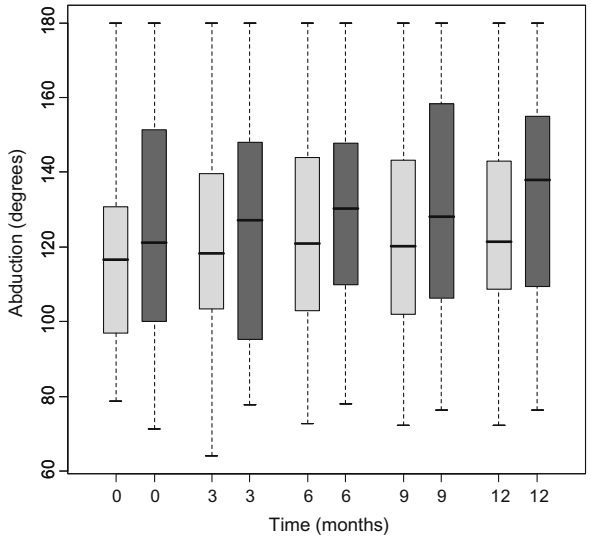

Fig. 2 – Box-plot of passive abduction of the shoulder by treatment group (light grey placebo, dark grey pentoxifylline) and visit.

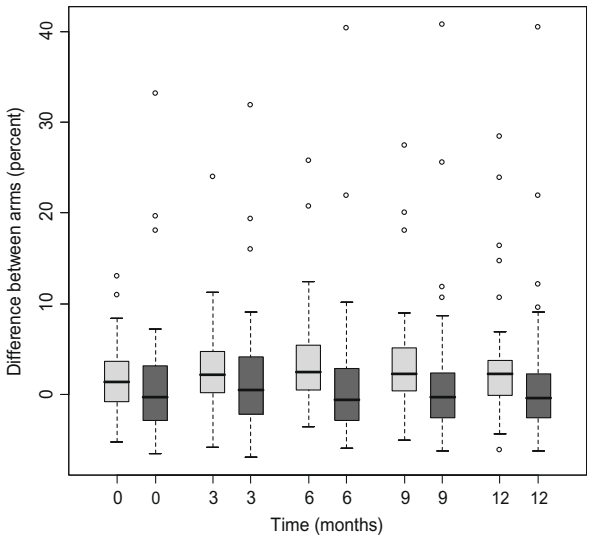

Fig. 3 – Box-plot of difference in volume between arms by treatment group (light grey placebo, dark grey pentoxifylline) and visit.

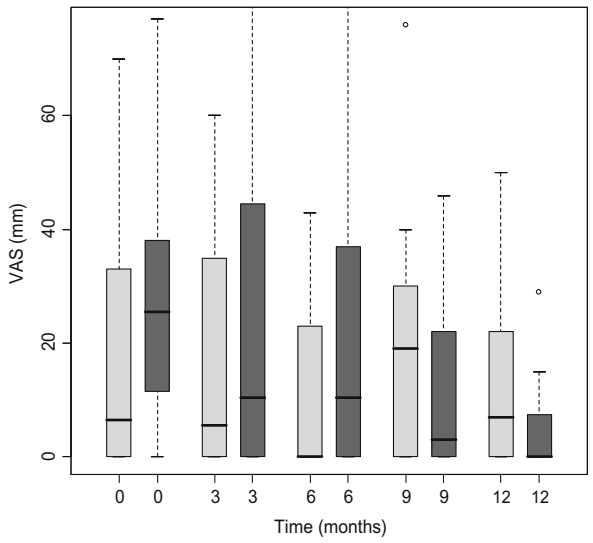

Fig. 4 – Box-plot of VAS for stiffness of the skin by treatment group (light grey placebo, dark grey pentoxifylline) and visit in the 38 patients reporting this phenomenon at least once during the study.

3.6. *Plasma concentration*

Plasma concentrations of pentoxifylline, R-M1 and S-M1 are given in Table 3. The measured point concentrations and metabolite to parent compound ratios are in agreement with what should be expected in patients with good compliance.[18]

4. Discussion

This study shows that daily doses of 1200 mg pentoxifylline in combination with 300 mg vitamin E are as safe as 300 mg vitamin E to use prophylactically and can reduce some side-effects from radiotherapy in women with breast cancer. Although our study was not dimensioned for safety, we observed no significant differences between the study groups in terms of safety, including disease recurrence, death and adverse events. Nausea was a common adverse event and is a well-known side-effect of pentoxifylline that usually lasts only for a few days. It had only a small impact in this study; two patients in the pentoxifylline group discontinued the treatment and one reduced the dose due to nausea. Two patients in the placebo group reduced the dose due to nausea. All patients will be followed up for at least four years after termination of pentoxifylline/placebo and vitamin E treatment to assess safety and efficacy.

We did not find any treatment effects on our primary effect parameter, abduction of the shoulder. When designing this study, we used our results from a previous study where we found a 17° median intra-individual decline in abduction from the end of radiotherapy to the follow-up visit 8 months later in patients treated with radiotherapy to the breast and axilla.[20] The patients were followed up for two years and the decline continued during this time. We therefore expected a reduction in passive abduction of the shoulder in both treatment groups. Instead, we found that shoulder abduction improved in both treatment groups. Changes in physiotherapy may have played a role in this improvement. Previously, an exercise programme that only included shoulder motion was used. Since then, all patients receive a training programme mostly focused on stretching the shoulder and breast area. Additionally, the radiation technique has been refined to diminish radiation-induced side-effects. All patients have an individualised three-dimensional dose plan based on CT. The target volume has been decreased mainly by omitting the axillary lymph nodes in level 1. This diminishes the radiation dose to muscle tissue around the caput humerus and tissue around the axilla. The discrepancies between the studies could be explained by one or a combination of both factors. A third possibility would be poor compliance, but 75/83 patients had good medication compliance as judged by tablet count, and the measured concentrations of pentoxifylline and metabolites in plasma are in agreement with what should be expected in patients with good compliance.[18] Another, but unlikely, explanation could be that vitamin E causes the improvement since all patients received 300 mg vitamin E daily.

RIF had been considered irreversible, but a few recent publications have shown that therapy with pentoxifylline and vitamin E may decrease or even reverse RIF.[7,21,22] Most of the studies are case reports or small uncontrolled studies; however, Delanian et al. performed a double-blind, placebo-controlled study in 24 women previously treated for breast cancer.[7] After 6 months of treatment, mean RIF surface regression was significant with combined pentoxifylline (800 mg/day) and vitamin E (1000U/day) treatment versus double placebo treatment (60% ± 11% versus 43% ± 17%). The treatment of pentoxifylline or vitamin E alone was ineffective (39% ± 37 versus 40% ± 32%).

We found that arm volume increased over time in the placebo group but not in the pentoxifylline group. The treatment

Table 3 – Plasma concentrations of pentoxifylline and its metabolites S-M1 and R-M1.

Compound		3 months	6 months	9 months	12 months
Ptx	Conc (ng/ml)	174 (72–234)	116 (78–214)	152 (80–230)	97 (60–134)
S-M1	Conc (ng/ml)	417 (250–645)	382 (239–525)	403 (249–586)	313 (208–596)
	Molar ratio S-M1/Ptx	2.54 (1.85–3.56)	2.87 (1.88–3.81)	2.85 (1.71–4.73)	3.71 (2.52–4.24)
R-M1	Conc (ng/ml)	15 (1–27)	15 (1–26)	15 (1–21)	3.5 (1–13)
	Molar ratio R-M1/Ptx	0.08 (0.04–0.12)	0.07 (0.03–0.12)	0.06 (0.02–0.14)	0.05 (0.02–0.11)
	Molar ratio R-M1/S-M1	0.03 (0.01–0.05)	0.03 (0.01–0.05)	0.03 (0.01–0.04)	0.01 (0.00–0.03)

appears to have no effect on the patients having more than 5% difference in arm volume at the start.

We found no significant effect on the LENT-SOMA total score. We investigated the sub-scores for subjective pain, management pain and objective fibrosis separately since we considered these parameters most relevant to the patients. Subjective pain decreased for the patients in the placebo group but not in the pentoxifylline group and management pain increased over time in the pentoxifylline group but not in the placebo group. This difference was significant between the groups at 12 months suggesting that the pentoxifylline group had more intense medication for pain. This was an unexpected result for which we have no good explanation.

We also found that the VAS score for pain described as stiffness in the skin significantly decreased in the pentoxifylline group during the treatment time ($p = 0.0003$), but not in the placebo group ($p = 0.97$). The sense of stiffness may be a harbinger of reduced abduction of the shoulder. When comparing scores for VAS stiffness to abduction of the shoulder, it appears that high VAS stiffness score is connected to lower degrees of abduction, i.e. less ability to move the arm.

Prior to initiation of this study, no other prophylactic studies with pentoxifylline and vitamin E were published. Since interaction of pentoxifylline and vitamin E with the efficacy of radiation was unknown, for safety reasons we decided that the radiotherapy should be completed before the patients were included in the study. Since then, there have been two other studies published using pentoxifylline to prevent radiation-induced side-effects. Ozturk et al. administered 400 mg pentoxifylline t.i.d. during the entire radiotherapy in order to prevent radiation-induced lung toxicity in patients with lung or breast cancer.[23] A significant protective effect of pentoxifylline compared with that of placebo was reported for both early and late lung radiotoxicities. In another study, 400 mg pentoxifylline t.i.d. was given during radiotherapy to patients with squamous cell carcinoma of the head and neck.[24] Late skin changes, fibrosis and soft tissue necrosis were more severe in the control group than in the pentoxifylline group. These studies indicate that it may be safe to give pentoxifylline during the radiotherapy.

We initially chose 500 mg vitamin E b.i.d. since the previous studies have used this dosage. Just after patient recruitment had started, Miller et al. published a meta-analysis that showed that daily doses of vitamin E > = 400 IU (400 mg) may increase all-cause mortality and it should be avoided.[25] The recent HOPE and HOPE-TOO also showed that in patients with vascular disease or diabetes mellitus, long-term treatment with 400 mg vitamin E may increase the risk of heart failure.[26] Whether these results implied an increased risk for our patient population was not clear, but for safety reasons, we decided to reduce the vitamin E dose to 300 mg since this is a prophylactic study with long-treatment time. After completion of the treatment period of this study, a meta-analysis showed that vitamin E intake is unlikely to affect mortality regardless of dose.[27]

In conclusion, the combination of pentoxifylline and vitamin E is safe and can be used to prevent some radiation-induced side-effects such as the development of increased arm volume after a post-operative irradiation. We did not find any significant effects on abduction of the shoulder but we found that VAS for stiffness in the skin decreased in the pentoxifylline group.

Conflicts of interest statement

MM, PH, KJ, CJ, FK, PM and AW have no conflicts of interest to declare. EK owns stock in AstraZeneca.

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