Med Oncol (2007) 24:308–311
DOI 10.1007/s12032-007-0006-z

ORIGINAL ARTICLE

Pentoxifylline and alpha-tocopherol in prevention of radiation-induced lung toxicity in patients with lung cancer

Cem H. Misirlioglu · Taciser Demirkasimoglu · Bulent Kucukplakci · Ergun Sanri · Kadri Altundag

Received: 9 January 2007 / Accepted: 22 February 2007 / Published online: 22 May 2007

Abstract Combined use of pentoxifylline and vitamin E is reported to reduce radiation-induced toxicity in normal tissues at molecular level. We plan to evaluate the role of combined use of pentoxifylline (PTX) and alpha-tocopherol (vitamin E; Vit E) for minimizing radiation-induced lung toxicity. A total of 91 lung cancer patients were randomized. Among them, 44 received PTX (400 mg three times a day orally and Vit E 300 mg twice a day orally during the entire period of radiotherapy. PTX and Vit E were further administered at doses of 400 mg once a day and 300 mg once a day, respectively for 3 months after radiotherapy. A total of 47 patients were assigned as a control group. Radiation related acute and late toxicities are evaluated by radiation RTOG/EORTC toxicity scale. Median age was 59 (range, 41–75). Median follow-up was 13 months (range, 3–28 months). Radiation-induced lung toxicity was more frequent in control group for all phases than in pentoxifylline and alpha-tocopherol group (acute phase, $P = 0.042$, subacute phase $P = 0.0001$, late phase $P = 0.256$). PTX and Vit E combination might be considered especially in patients with lung cancer who receive concurrent chemo-radiotherapy, or have a poor respiratory function tests.

Keywords Lung cancer · Radiation-induced lung toxicity · Pentoxifylline · Alpha-tocopherol

C. H. Misirlioglu · T. Demirkasimoglu · B. Kucukplakci · E. Sanri
Department of Radiation Oncology, Ankara Oncology Hospital, Ankara, Turkey

K. Altundag (✉)
Department of Medical Oncology, Hacettepe University Institute of Oncology, 06100 Ankara, Turkey
e-mail: altundag66@yahoo.com

Introduction

Radiation-induced lung toxicity (RILT) is a rare morbid complication of radiotherapy. Radiotherapy damage to normal lung tissue results in intraalveolar edema, congestion, and local inflammation with further destruction of alveolar capillary structure. Consequently, these reactions may induce functional disabilities or scar formation depending on the severity of the damage. The range of respiratory compromise can extend from pneumonitis to fibrosis, with varying degrees of chronic pulmonary decompensation manifesting years after the initial cancer therapy. Clinically patients are presented with dyspnea, dry cough, chest pain and/or fever is diagnosed radiologically and clinically at a frequency of 65% and 15–30%, respectively in lung cancer patients [1–4]. Since concomitant chemotherapy is commonly used, this complication appears to be more frequent in recent years [5]. Pentoxifylline (PTX) is classically used as peripheric vasodilator. At molecular level, it inhibits the activation of interleukin-1 and tumor necrosis factor-alpha, then in turn increases fibrinolytic activity through increased secretion of prostocyclines [6–8]. Used as an anti-oxidant agent in clinical practice, alpha-tocopherol (vitamin E; Vit E) had an antifibrotic effect by inhibiting overexpression of transforming growth factor-beta that have a role in the process of fibrosis development. Therefore, it is assumed that Vit E may prevent radiation-induced tissue damage [7, 9].

Preclinical studies demonstrated the role of PTX and Vit E in prevention of RILT. However, studies reported in the literature for the effect of these agents in prevention of RILT were either experimental studies or used only one agent on clinical basis. Therefore, we decided to look at the combined affect of these two agents in lung cancer patients having radiotherapy for primary lesion. Using both agents

together, we aimed to reduce RILT to minimum, and consequently to increase patient's quality of life.

Materials and methods

Eligibility and pre-treatment assessment

After the Turkish Ministry of Health Ethical Committee and the Ethics Committee of our hospital gave written permission, we initiated the study. All patients were provided an informed written consent before they enrolled in this study, in accordance with the declaration of Helsinki. Eligibility criteria include; patients with localized non-small cell lung cancer (NSCLC) or small-cell lung cancer (SCLC) who were planned to receive curative radiotherapy at a dose of at least 4,000 cGy to the lung, patients with ECOG performance status 0–2, patients at age of 40–80 years without having bleeding diathesis or any significant comorbid diseases such as coronary artery disease or chronic obstructive lung disease. The patients who developed a grade 3–4 toxicity, or have a progression during the treatment period were excluded from the study.

A total of 91 patients with a diagnosis of lung cancer who had a ECOG performance status 0–2 and had a plan to receive radiotherapy to primary tumor were enrolled in the study between September 2002 and October 2003 at Ankara Oncology Hospital. Among them, 44 received PTX (400 mg three times a day orally and Vit E 300 mg twice a day orally during the entire period of radiotherapy. PTX and Vit E were further administered at doses of 400 mg once a day and 300 mg once a day, respectively for 3 months after radiotherapy. Forty-seven patients were assigned as a control group.

Radiotherapy was initially delivered to primary tumor and regional lymphatics at first phase, and in the second phase only primary tumor was irradiated. All patients had received at least 4,000 cGy radiotherapy.

Clinical assessment

Follow-up visits after the completion of radiotherapy was performed at every 1.5 month's periods for 3 months, then at every 3-months period. Study was completed in December-2004 and analysis was done based on this date. Acute and late side effects of radiation were evaluated by using the RTOG/EORTC toxicity scale. At each follow-up visit, in addition to clinical evaluation, chest X-ray, pulmonary function tests (FEV1, FVC, FEV1/FVC), complete blood count and essential biochemical tests were performed. Primary lesion was assessed by thoracic computed tomography at 3, 6, and 12 months after the completion of radiotherapy. At each visit, in addition to physical examination, detailed history that may be related to RILT was taken. To follow the changes in hemostasis, prothrombin time was measured at the beginning of the treatment and each follow-up visit. All side effects such as pain, dysphagia, nausea vomiting, leukopenia, anemia, thrombocytopenia, skin reactions, fatigue, and hypotension that may occur during the radiotherapy period were noted according to common toxicity criteria-2. Pneumonic presentation observed at acute phase and pleural thickening and fibrosis observed at late phase by computed tomography was also taken into consideration. Lung function test measuring FEV1, FVC, FEV1/FVC was performed at the beginning of the treatment and each follow-up visit.

The patients were randomly assigned to two groups based on stage and pathological diagnosis. Acute phase evaluation (period between the completion of radiotherapy and second post-radiotherapy month) was performed for 91 patients, third post-radiotherapy (subacute phase) month evaluation for 69 patients, sixth month post-radiotherapy (subacute phase) evaluation for 27 patients, and first year post-radiotherapy (late phase) evaluation for 25 patients We used Mann–Whitney *U* test and Willcoxon test for statistical analysis.

Results

Patient characteristics

Initially 114 patients were enrolled into study. A total of 23 patients were excluded from study for following reasons: inappropriate use of study drugs, death occurred before the first follow-up visit, and lost the follow-up due to unknown reason. For remaining 91 patients, median age was 59 (range, 41–75). Median follow-up time was 11 month (range, 3–28). Patient characteristics are summarized in Table 1. Eighty-six patients were male. Fifty-nine patients (65%) with NSCLC had a stage IIIB disease.

Toxicity

TX dose was reduced in half in 10 patients for grade 3–4 nausea vomiting. One patient developed allergic reaction probably related to PTX at the completion of radiotherapy treatment. This patient did not take maintenance treatment. There were no significant side effects observed in the study attributed to Vit E.

Clinical efficacy

Radiotherapy dose, volume, fractionation volume, type of radiotherapy applicator, chemotherapy history, age, performance status, stage, tumor pathology, and smoking

Table 1 Patient's characteristic in two groups ($n = 91$)

Patient characteristics	PTX + Vit E group ($n = 44$)	Control group ($n = 47$)	P value
Gender			
Male	43	43	0.192
Female	1	4	
Age			
Mean	58	60	0.894
Median	59	59	
Smoking history			
No	0	2	0.171
Modest	1	5	
Severe	43	40	
ECOG PS			
0	7	11	0.130
1	28	20	
2	9	16	
Stage			
IIIA NSCLC	9	10	0.718
IIIB NSCLC	30	29	
Limited SCLC	5	8	
Pathology			
NSCLC	39	39	0.330
SCLC	5	8	
RT dose (median) cGy	5,500 ± 7.1	5,300 ± 7.3	0.166
RT volume (mean) cm^2	139 ± 29.7	148 ± 37.6	0.227
RT fraction			
200 cGy/day	37	33	0.116
300 cGy/day	7	14	
RT device			
Co 60	23	17	0.122
Linac	21	30	
CT			
Yes	30	37	0.254
No	14	10	

RT, Radiotherapy; CT, chemotherapy; Co 60, Cobalt 60;Vit E, Vitamin E; PTX, pentoxifylline; Linac, linear accelerator; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; PS, performance status

history were comparable in both groups (Table 1). In acute phase, total 23 patients (25%) developed RILT. Among them, seven patients (7.5%) were in PTX + Vit E group. RILT was observed in 16% of patients in PTX and Vit E group and 30.5% of patients in control group at late phase.

RILT was more frequent in control group for all phases than in PTX and Vit E group (acute phase, $P = 0.042$, subacute phase $P = 0.0001$, late phase $P = 0.256$). This statistical difference between groups became insignificant after the ninth month follow-up. Frequency of RILT observed in acute phase for patients in treatment groups did not change in subacute and late phase. In contrast, this frequency significantly increased when the patients in control group came to subacute and late phase (subacute phase, $P = 0.0001$, late phase, $P = 0.02$).

Discussion

Having known the fact that currently there is no satisfactory treatment for RILT, PTX and Vit E combination prophylaxis might prevent RILT in lung cancer patients having been receiving radiotherapy without any significant side effects.

For the last 15 years, its positive effect on prevention of radiation-induced fibrosis has been shown by multiple experimental and clinical studies. Preclinical studies supported that PTX improve and reduce the late radiation related side effects. However, clinical data is scarce. Some reports indicate that PTX and Vit E combination may be more effective for prevention of these side-effects [7, 9, 10]. Likewise, Dion et al. in their study found that PTX improved soft tissue necrosis caused by radiation in 12 patients [8]. In another study by Dion et al. performed on rats, PTX decreased late effects of radiation-induced toxicity developed on their extremities [11]. Futran et al. also showed the effectiveness of PTX in head and neck cancer patients who developed radiation induced soft tissue necrosis and fibrosis [12]. Furthermore, PTX showed a modest effect in the treatment of trismus developing as a consequence of radiation induced fibrosis in head and neck cancer patients [13]. In a prophylaxy study with PTX, Aygenc and their colleagues showed its effectiveness in decreasing severity and frequency of radiation induced skin changes, fibrosis, and tissue necrosis [14]. Ozturk et al. [4] reported in their randomized double-blind clinical trial that the pentoxyfylline was beneficial prophylactically in preventing radiation pneumonia in lung and breast cancer patients. In animal study by Lefaix et al. [10], PTX alone compared to PTX and Vit E for their efficacy in the fibrosis control. The results showed that combination group was more effective than PTX alone group. The same authors did the same study in patients with fibrosis and showed the synergistic effect of these agents [7, 9, 15].

The severity and frequency of RILT are associated with treatment volume, total dose, fractionation volume and quantity, and radiation quality. Moreover, radiation induced lung toxicity is more pronounced when radiotherapy is given concurrently with chemotherapy [2, 3, 16, 17]. In our study, there was no difference present between the groups in respect to total chemotherapy dose. However, chemotherapy regimens were somewhat different in two groups. Smoking history is accepted as a risk factor for the development of RILT. Since the most cases (27/29) in our

study had a smoking history, we could not estimate its impact on RILT.

All RILT cases in our study was observed to be restricted to the radiation port. Some cases in the literature reported that RILT might develop outside the radiation port. This might be related to hypersensitivity reactions [17]. Positive effect of PTX and Vit E was more pronounced at third and sixth month period, but less pronounced at acute phase. This positive effect faded away when the patients came to follow-up visit at ninth month and twelfth month follow-up.

Having known the fact that RILT may result in detrimental effects on lung with worsening the quality of life and currently there is no effective treatment resolve this pathology, PTX and Vit E combination might be considered especially in patients with lung cancer who receive concurrent chemo-radiotherapy, or have a poor respiratory function tests.

References

1. McDonald S, Rubin P, Phillips TL, Marks LB. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. Int J Radiat Oncol Biol Phys 1995;31:1187–203.
2. Robnett TJ, et al. Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2000;48:89–94.
3. Inoue A, et al. Radiation pneumonitis in lung cancer patients: a retrospective study of risk factors and the long-term prognosis. Int J Radiat Oncol Biol Phys 2001;49:649–55.
4. Ozturk B, Egehan I, Atavci S, Kitapci M. Pentoxıfylline in prevention of radiation-induced lung toxicity in patients with breast and lung cancer: a double-blind randomized trial. Int J Radiat Oncol Biol Phys 2004;58:213–9.
5. Rosen II, et al. Correlation between lung fibrosis and radiation therapy dose after concurrent radiation therapy and chemotherapy for limited small cell lung cancer. Radiology 2001;221:614–22.
6. Rube CE, et al. Modulation of radiation-induced tumour necrosis factor a (TNF-a) expression in the lung tissue by pentoxifylline. Radiother Oncol 2002;64:177–88.
7. Delanian S, Lefaix J-L. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. Radiother Oncol 2004;73:119–31.
8. Dion MW, et al. Preliminary results of a pilot study of pentoxifylline in the treatment of late radiation soft tissue necrosis. Int J Radiat Oncol Biol Phys 1990;19:401–7.
9. Delanian S, Balla-Mekias S, Lefaix JL. Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. J Clin Oncol 1999;17:3283–90.
10. Lefaix JL, et al. Striking regression of subcutaneous fibrosis induced by high doses of gamma rays using a combination of pentoxifylline and alpha-tocopherol: an experimental study. Int J Radiat Oncol Biol Phys 1999;43:839–47.
11. Dion MW, Hussey DH, Osborne JW. The effect of pentoxiflylline on early and late radiation injury following fractionated irradiation in C3H mice. Int J Radiat Oncol Biol Phys 1989;17:101–7.
12. Futran ND, Trotti A, Gwede C. Pentoxifylline in the treatment of radiation-related soft tissue injury: preliminary observations. Laryngoscope 1997;107:391–5.
13. Chua DT, Lo C, Yuen J, Foo YC. A pilot study of pentoxifylline in the treatment of radiation-induced trismus. Am J Clin Oncol 2001;24:366–9.
14. Aygenc E, et al. Prophylactic effect of pentoxifylline on radiotherapy complications: a clinical study. Otolaryngol Head Neck Surg 2004;130:351–6.
15. Delanian S, Porcher R, Balla-Mekias S, Lefaix J-L. Randomized placebo-controlled trial combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. J Clin Oncol 2003;21:2545–50.
16. Makimoto T, et al. Risk factors for severe radiation pneumonitis in lung cancer. Jpn J Clin Oncol 1999;29:192–7.
17. Miller KL, Shafman TD, Marks LB. A practical approach to pulmonary risk assessment in the radiotherapy of lung cancer. Semin Radiat Oncol 2004;14:298–307.