Effect of Concomitant Use of Pentoxifylline and Alpha-Tocopherol with Radiotherapy on the Clinical Outcome of Patients with Stage IIIIB Non-Small Cell Lung Cancer

A Randomized Prospective Clinical Trial

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Abstract

We evaluated the effects of pentoxifylline (PTX) and alpha-tocopherol on the clinical outcome of 66 patients with stage IIIIB non-small cell lung cancer in a randomized clinical trial. All patients received 46 Gy of external radiotherapy to the primary tumor and regional lymph nodes, with an additional 14-Gy dose to the primary tumor. Thirty-three of the 66 patients also received PTX (400 mg, three times daily) and alpha-tocopherol (300 mg, twice daily) during radiotherapy, followed by 400 mg of PTX and 300 mg of alpha-tocopherol daily for 3 mo after radiotherapy. The remaining 33 patients (control group) received radiotherapy only. After a mean follow-up time of 12 mo, 18 patients remained alive. During follow-up, there were local recurrences in 14 patients and distant metastases in 18 patients. In patients who received PTX and alpha-tocopherol, 1- and 2-yr overall survival rates were 55% and 30%, respectively, and median survival was 18 mo. In control patients, 1- and 2-yr overall survival rates were 40% and 14%, respectively, with a median survival of 10 mo. These differences were statistically significant (p = 0.0175). In patients who received PTX and alpha-tocopherol, progression-free survival rates for 1 and 2 yr were 48% and 23%, respectively; median survival was 12 mo. In the control group, the corresponding rates were 24% and 18%; median survival was 8 mo (p = 0.0223). We conclude that the use of PTX and alpha-tocopherol combined with radiotherapy offers a possible survival advantage in this patient population.

Key Words: Non-small cell lung cancer, locally advanced; pentoxifylline; alpha-tocopherol; radiotherapy; chemotherapy.

Introduction

Locally advanced non-small cell lung cancer (NSCLC) is treated with radiotherapy, chemotherapy, and (rarely) with surgery or with combined modality therapy. Long-term survival rates are between 5% and 20% (1). To increase the benefit
from radiotherapy, radiosensitizing agents are commonly used. The most important dose-limiting factor in lung cancer treatment is radiation toxicity. Some patients may suffer more from radiation toxicity than from their tumor.

The drug pentoxifylline (PTX) inhibits the activation of cytokines such as interleukin-1 and TNF-α; therefore, fibrinolytic activity increases as the releasing of prostacyclines increases. Alpha-tocopherol (vitamin E) inhibits the overexpression of TGF-β1, which causes fibrosis. This antifibrotic effect may therefore prevent radiation-induced damage (2,3). PTX also regulates the peripheral blood stream, so hypoxia of the tumor decreases and the benefit of radiation increases (3).

We evaluated the antifibrinolytic and radiosensitizing effects of PTX and the antioxidant effect of vitamin E in patients with stage IIIB NSCLC in a randomized clinical trial.

Patients and Methods

Sixty-six patients with a diagnosis of stage IIIB NSCLC cancer were enrolled in the study between September 2002 and October 2003 at Ankara Oncology Hospital. Eligibility criteria included a diagnosis of localized NSCLC, a plan to receive curative radiotherapy, an ECOG performance status of 0–2, patient age of 40–80 yr, no bleeding diathesis, and no significant co-morbidities such as coronary artery disease or chronic obstructive lung disease.

Radiotherapy at a dose of 46 Gy was initially delivered to the primary tumor and regional lymphatics during the first phase of treatment; in the second phase, the primary tumor received an additional 14-Gy dose. No patient received concomitant chemotherapy. Chemotherapy was given either as neoadjuvant treatment or after radiotherapy.

Of the 66 patients, 33 received PTX (400 mg, three times daily) and alpha-tocopherol (300 mg, twice daily) during the entire period of radiotherapy and then 400 mg of PTX and 300 mg of alpha-tocopherol daily for 3 mo after radiotherapy. The remaining 33 patients (control group) received radiotherapy only. After the completion of radiotherapy, patients received follow-up evaluation at 1.5-mo intervals for 3 mo, then at 3-mo intervals. At each follow-up, patients underwent clinical evaluation, chest X-ray, pulmonary function tests (FEV1, FVC, FEV1/FVC), complete blood count, and biochemical tests. The primary lesion was assessed by thoracal-computed tomography at 3, 6, and 12 mo after the completion of radiotherapy.

Treatment response was defined as follows: a complete response was defined as complete tumor disappearance. A partial response required a reduction of at least 50% in the volume of the tumor. Stable disease was defined as no change or <50% reduction, and progressive disease was defined as an increase in the volume of the initial tumor volume. The study was completed in December 2004, and analysis was performed based on this date. Treatment failure was analyzed for local, regional, and distant metastasis. Local recurrence was defined as any recurrence of the primary tumor, including persistent disease after initial treatment. Regrowing or newly developed mediastinal or supraclavicular lymphadenopathy was defined as regional recurrence, and distant metastasis as any recurrence of systemic organs. The survival time was counted from the day of randomization to the date of the diagnosis of recurrence, death, or the last follow-up. Patients were censored for progression-free survival analysis if they were progression-free at the last contact (or died without disease). Statistical analysis was performed by using the SPSS 11.5 program. Survival curves were constructed using the Kaplan–Meier method and compared using a log-rank test.

The study was approved by the Turkish Ministry of Health Ethical Committee and the Ethics Committee of our hospital. All patients provided informed written consent before they enrolled in this study.

Results

Three women and 63 men were included. Median age was 59 yr (range, 41–75). All but one of the 66 patients had a history of smoking. Coughing, dyspnea, and pain were the major symptoms. Forty-seven patients received chemotherapy before or after radiotherapy. Performance status, weight loss, age, radiotherapy dose, radiotherapy total time, pathologic diagnosis, and chemotherapy history in both groups