Comparision of Radiochemotherapy Applications that Committing with Two Different Chemotherapies Route in Locally Advanced Lung Cancer

Hilal Kiziltunc Ozmen[1], Orhan Sezen[1], Meryem Aktan[2], Burak Erdemci[1], Burcu Sağlam Alan[3], Mustafa Vecdi Ertekin[4], Sinan Ezirmik[4]

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[1]Department of Radiation Oncology, Ataturk University School of Medicine, Erzurum, Turkey
[2]Department of Radiation Oncology, Necmettin Erbakan University School of Medicine, Konya, Turkey
[3]Department of Radiation Oncology, Antalya Training and Research Hospital, Antalya, Turkey
[4]Department of Radiation Oncology, Nisantasi University School of Medicine, Istanbul, Turkey
[5]Department of Radiation Oncology, Ataturk Public Hospital, Balıkesir, Turkey

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Correspondence to: Hilal Kiziltunc Ozmen
E-mail: hilal.kiziltunc@atauni.edu.tr

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ABSTRACT

Objective: This study investigated pre- and post-treatment tumor and lymph node dimension response rates and differences between side-effect profiles in patients with locally advanced inoperable nonsmall-cell lung cancer (NSCLC) receiving radiotherapy (RT) and concurrent chemotherapy (CT).

Materials and Methods: A total of 30 inoperable patients who had not previously received RT and having a mean age of 58.73±8.65 years with sufficient hematological reserves and normal hepatic and renal functions were included in the study. Those with pleural effusion, supraventricular lymph node metastasis, and N3 lymph node involvement were excluded. Group I (n=15) received a 21-day 75 mg/m^2 cisplatin (D1) and 15 mg/m^2 vinorelbine (D1, D8), whereas Group II (n=15) received 45 mg/m2 paclitaxel and AUC2 carboplatin weekly. RT was administered using a linear accelerator device with the 3D conformal RT technique at 6-18 MV energy with a 1.8-2 Gy fraction for 6-7 weeks.

Results: Patients were randomized into Group I receiving RT and concurrent cisplatin–vinorelbine and Group II receiving weekly paclitaxel–carboplatin CT. Pre- and post-treatment tumor and lymph node dimensions significantly differed in both groups ($p<0.001$ and $p<0.01$, respectively). No significant change was observed in post-RT tumor and lymph node dimensions in terms of applied CT regimens ($p>0.05$).

Conclusion: The significant response achieved with concurrent RT and CT in groups I and II in the local advanced stage of NSCLC is important for local tumor control. Responses to treatment in the group of two arms did not differ.

Keywords: Non small cell lung cancer, chemotherapy, radiotherapy

Introduction

Cancer remains an important health problem with regard to the inconclusive nature of basic therapeutic principles and cost. As in the rest of the world, lung cancer is the most common type of cancer in Turkey with the highest mortality rate. The primary cause of lung cancer is smoking. Overall, 90% of men and 75%–80% of women with lung cancer in the USA have been identified as smokers. Nonsmall-cell histology constitutes approximately 80% of all lung cancers [1], and 25%–40% of patients with nonsmall-cell cancer (NSCLC) have advanced local Stage III disease at the time of diagnosis [2]. Majority of patients with Stage III NSCLC are not suitable for surgical resection and are generally treated with the combination of chemotherapy (CT) and radiotherapy (RT) [3]. Although CT is regarded as the standard therapeutic approach in patients with local advanced inoperable NSCLC, the order of administration of RT and CT is still uncertain [4]. Inturn approach is largely associated with the eradication of systemic metastases, whereas better local control in patients treated with concurrent chemoradiotherapy results in better survival [4].

This study aimed to investigate differences in radiological response rates and side-effect profiles in patients with locally advanced inoperable NSCLC receiving RT and concurrently receiving cisplatin–vinorelbine and paclitaxel–carboplatin chemotherapies.

Materials and Methods

This study has been conducted with the approval of the Ethics Committee of the Ataturk University Medical School (protocol number: B.30.2.ATA.0.01.00/91). The inclusion criteria were as

follows: age 40-80 years, with Karnofsky performance status of ≥70%, with cytologically or histologically confirmed locally advanced NSCLC without possibility of surgical resection, without previously receiving RT, without other primary lesion, with radiologically measurable disease (posterioanterior (PA) pulmonary x-ray or thoracic computerized tomography), with sufficient hematological reserves (Hgb≥10 g/dL, NE≥2.0, Plt≥100/nL), and with normal hepatic [serum bilirubin level=1.5×upper limit of normal (ULN), Alanine amino transferase (ALT) and Aspartate amino transferase (AST)=3×ULN] and renal (serum creatinine=1.5×ULN) functions. Patients not meeting the inclusion criteria and those with pleural effusion at the time of presentation, supraclavicular lymph node metastasis, or N3 disease were excluded. One of 32 patients presenting to the radiology oncology clinic for pulmonary RT was excluded because he refused receiving CT and other one because of cardiac contraindication. Finally, the study was conducted on 30 patients.

Patients were randomized into 2 CT groups. RT was started on day 1 in the CT patients (Group I, n=15; Group II, n=15). Patients in Group I received 2 courses of CT. Group I CT consisted of 75 mg/m^2 cisplatin (D1) and 15 mg/m^2 vinorelbine (D1, D8) administered once every 21 days. Cisplatin was first dissolved in 1000 mL of 0.9% isotonic solution and administered intravenously (iv) in the form of 4-h infusion, whereas vinorelbine was dissolved in 100 mL of 0.9% isotonic solution and administered iv as 30-min infusion. Group II CT consisted of weekly 45 mg/m^2 paclitaxel and carboplatin AUC2. Paclitaxel was first dissolved in 1000 mL of 0.9% isotonic solution and was further administered iv as 1.5-h infusion, whereas carboplatin was dissolved in 100 mL of 0.9% isotonic solution and administered iv by 30-min infusion. RT was administered 5 days a week with a 1.8-2 Gy fraction (63.3 Gy for Group I and 61.1 Gy for Group II) for 6-7 weeks using 6-18 MV energy with a linear accelerator (Siemens-Primus 2002, Germany) (Table 1). The same RT technique was employed in both groups.

Statistical Analysis

Data analysis was performed using the The Statistical Package for the Social Sciences (SPSS) 19.0 statistical software (IBM Corp.; Armonk, NY, USA). Comparisons between independent groups were performed using the Mann–Whitney U test, whereas the Wilcoxon signed rank test was used to compare independent groups. p values of <0.05 were regarded as statistically significant.

Table 1. Characteristics of cases receiving radiotherapy by chemotherapy regimens

	Group-I (C-V) (x±SD) n=15	Group-II (P-Cp) (x±SD) n=15
Age (years)	60.8±6.0	56.7±10.4
Smoking history (years)	36.0±9.2	33.9±12.1
Length of treatment (months)	6.5±4.1	8.4±8.2
RT dose (Gy)	63.3±2.9	61.1±10.0
Initial weight (kg)	71.3±10.5	72.0±13.0
Final weight (kg)	69.6±10.4	70.8±12.8

RT: radiotherapy; SD: standart deviation; C: cisplatin; V: Vinorelbine; P:Paclitaxel; Cp: Carboplatin

Results

Patients' demographic data are shown in Table 1, and changes in tumor and lymph node dimensions are shown in Table 2. The mean age of patients enrolled in the study was 58.73±8.65 years, and all were men. The most common histopathological subtype was squamous cell carcinoma in 18 patients (60%). Other histopathological subtypes were NSCLC of uncertain subtype in 7 patients (23.3%) and adenocarcinoma in 5 patients (16.6%). Smoking history was observed in 100% of the patients and in the family of 20%. The 2 groups were similar in terms of performance status, pathological distribution, and initial symptoms. CT was administered to all patients, except for one patient in Group II (mortality occurred at day 15 of treatment). Patients in Group I received a mean of 2 courses of CT concurrently with RT, whereas patients in Group 2 received a mean of 6 courses of chemotherapy.

Liver metastasis was observed in 1 patient in Group II, but no metastasis was determined in Group I. The follow-up period ranged between 15 days and 24 months, and response evaluation was performed based on check-ups 2 months after CT. Approximately 21% of patients survived during this follow-up period and 80% died. Hematological and nonhematological side effects were generally at tolerable levels. Esophagitis developed in 9 patients (60%) each in Group I [Grade I in 6 (66.7%) and Grade II in 3 (33.3%)] and Group II [Grade I in 5 (55.6%), Grade II in 3 (33.3%), and Grade III in 1 (11.1%)]. Neutropenia developed in 6 patients (40%) each in Group I [Grade I in 3 (50%) and Grade II in 3 (50%)] and Group II [Grade I in 5 (83.3%) and Grade II in 1 (16.7%)]. Grade II cutaneous reaction developed in 1 patient (13.3%) in Group I and in 2 patients (13.3%) in Group II. Nephrotoxicity developed in 1 patient (6.7%) in Group I but in none from Group II. Arrhythmia

Table 2. Changes in tumor and lymph node dimensions by chemotherapy regimen applied with radiotherapy

		Radiotherapy and Chemotherapy (C-V)		Radiotherapy and Chemotherapy (P-Cp)		TOTAL	
LESION TYPE	CHANGE IN LESION SIZE (%)	Number	Percentage	Number	Percentage	Number	Percentage
TUMOR	100% Decrease	1	6.7	2	13.3	3	10.0
	≥30% Decrease	12	80	11	73.3	23	76.7
	≥20% Increase	-	-	1	6.7	1	3.3
	<30% Decrease or <20% Increase	2	13.3	1	6.7	3	10.0
LYMPH NODE	100% Decrease	-	-	1	6.7	1	3.3
	≥30% Decrease	5	33.3	5	33.3	10	33.3
	≥20% Increase	-	-	-	-	-	-
	<30% Decrease or < 20% Increase	10	66.7	9	60	19	63.3

C: Cisplatin; V: Vinorelbine; P: Paclitaxel; Cp: Carboplatin

was observed in 1 patient (6.7%) in Group I but none from Group II.

Discussion

Cancer is a common health problem causing significant mortality and morbidity and poses an economic burden. Its development is a complex process, in whose etiology involves genetic, environmental, and dietary factors. In clinical practice, the form with the highest morality is lung cancer, and its development is particularly associated with smoking and genetic and various environmental factors [5-7].

The only known curative treatment for Stages I and II NSCLC is surgery; <30% of all patients with NSCLC are within operable limits upon the diagnosis. The standard approach for Stage III B NSCLC is combined RT and CT. A large number of patients with NSCLC are Stages III and IV when diagnosed [8]. Although the life expectancy of patients with advanced grade NSCLC is low, various studies have shown significant improvements in the mean survival, quality of life, and performance with combined CT [9-10]. Therefore, different chemotherapeutic agents have been used for the treatment of NSCLC, and objective response rates of 8%-20% have been obtained; this has increased to 20%-30% with cisplatin-containing combinations [9, 11]. With vinorelbine alone (30 mg/m^2/week), Le Chevalier et al. [12] achieved a 14% response rate, 31-week median survival, and a 30% 1-year survival rate, whereas with a combination of cisplatin (120 mg/m^2) and vinorelbine (30 mg/m^2/week), a 30% response rate, 40-week median survival, and a 35% 1-year survival rate were achieved [13]. Myelosuppression was reported as the primary toxicity. Grade 3–4 myelosuppression was observed in 79% of patients treated with combined cisplatin–vinorelbine therapy. In a phase III study, Depierrer et al. [14] compared vinorelbine alone and a cisplatin–vinorelbine combination in 231 patients and reported improved objective response rates (16% and 43%, respectively) and time to progression of disease (10 and 20 weeks, respectively); however, no changes were observed in the length of survival (32 and 33 weeks, respectively) [15]. In our study, partial and complete response for our treatment were achieved in 86.7% of patients in the cisplatin–vinorelbine group also receiving RT. The remaining 13.3% were assessed as having stable disease, without disease progression. In terms of lymph node response, 33.3% partial response was observed and the remaining 66.7% were assessed as having stable disease. Neutropenia developed in 6 (40%) patients: Grade I in 3 (50%) and Grade II in 3 (50%). No myelosuppression requiring interruption or discontinuation of treatment was encountered.

Various phase II studies on advanced NSCLC and paclitaxel have reported response rates of 21%-36%, and 1-year survival rates of 38%-41% [16-19]. Despite the low objective response rate of carboplatin (9%), the highest 1-year survival rates were achieved in a five-arm ECOG study comparing cisplatin combinations and analogs. A combination of carboplatin–etoposide was reported to yield the same response rates as the standard cisplatin–etoposide therapy and to cause less toxicity [20]. A ECOG study comprising 506 patients comparing a paclitaxel–cisplatin combination with standard cisplatin–etoposide therapy achieved higher response rates and longer survival with the paclitaxel–cisplatin combination [21]. It has been suggested that taxane combinations will predominate in the future and novel combinations will be available with this group of drugs [22]. Studies have shown that toxicity is generally low with the paclitaxel–carboplatin combination and bone marrow toxicity is dose-dependent and shortlived and can be easily controlled with colony-stimulating factors [23-27]. One large European–Canadian study showed that myelotoxicity decreased as paclitaxel infusion time was reduced [28]. For all these reasons, a paclitaxel–carboplatin combination with paclitaxel was administered through the 1.5-h infusion in our study. A total response rate, both partial and complete, was 86.6% in the group receiving paclitaxel–carboplatin with RT. One patient (6.7%) was assessed as having stable disease, whereas disease progression was seen in another patient (6.7%). In terms of lymph node response, 6.7% of patients had complete response and 33.3% had partial response, whereas 60% of patients were regarded as having stable disease. Neutropenia developed in 6 patients (40%) in this group: Grade I in 5 (83.3%) and Grade II in 1 (16.7%). No myelosuppression requiring interruption or discontinuation of treatment occurred. No thrombocytopenia was also observed.

In conclusion, the significant response achieved with cisplatin–vinorelbine and paclitaxel–carboplatin chemotherapies concurrently administered with RT for the treatment of locally advanced inoperable NSCLC is significant in local tumor control. No difference was observed in the response rates. While selecting the appropriate chemotherapeutic regimen, separate evaluation should be performed for each patient, considering factors such as suitability for effect mechanisms, anticipated tolerability and side-effect profile, ease of application, length of application, and cost. Further studies comparing chemotherapeutic regimens with long post-chemoradiotherapy follow-up will be useful for systemic control.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Ataturk University Medical School (protocol number: B.30.2.ATA.0.01.00/91).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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