Original Article

Definitive chemoradiotherapy in Stage III nonsmall cell lung cancer: Turkey experience

Ufuk Yılmaz, Ulku Yılmaz[1], Zehra Yasar[2], Esra Korkmaz Kıraklı[3], Sukran Ulger[4], Yasemin Ozdogan, Nilgun Yilmaz Demirci[5], Serhat Erol, Ilker Ozdogan[3], Burcu Sahin[6], Deniz Koksal[7], Cimen Akcay[3]

Departments of Chest Diseases and [3]Radiation Oncology, Suat Seren Chest Disease and Surgery Training and Research Hospital, İzmir, [1]Department of Chest Diseases, Atatürk Chest Disease and Surgery Training and Research Hospital, Departments of [4]Radiation Oncology and [5]Chest Diseases, Gazi University School of Medicine, [6]Department of Radiology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, [7]Department of Chest Diseases, Hacettepe University School of Medicine, Ankara, [2]Department of Chest Diseases, Abant Izzet Baysal University School of Medicine, Bolu, Turkey

For correspondence: Dr. Zehra Yasar, Department of Chest Diseases, Abant Izzet Baysal University School of Medicine, Golkoy, Bolu, Turkey. E-mail: zehraasuk@hotmail.com

ABSTRACT

Aim: Concurrent chemoradiotherapy (CRT) is the standard therapy for patients with unresectable Stage III nonsmall cell lung cancer (NSCLC). The aim of this study was to assess the efficacy and safety of concurrent CRT in unresectable Stage III NSCLC in Turkey.

Patients and Methods: The study included 82 patients with histologically proven unresectable Stage III NSCLC, Eastern Cooperative Oncology Group performance status 0–1, who received concurrent CRT in two different referral centers. Treatment consisted of two cycles of cisplatin at 50 mg/m^2 on days 1, 8, 29, and 36 and etoposide 50 mg/m^2 between days 1 and 5, 29–33 and concurrent radiotherapy administered once daily, 1.8–2.0 Gy per fraction, at a total dose of 60–66 Gy.

Results: The stages of the patients were Stage IIIA in 39 (47.5%) and IIIB in 43 (52.5%) patients. Complete and partial responses were achieved in 15 (18.2%) and 31 (37.8%) of the patients, respectively. Twenty-eight (34.2%) patients had stable disease and 8 (9.8) had progressive disease. Forty-one (50%) patients recurred during follow-up. The primary site of recurrence was as distant metastasis in 19 (23.2%) patients. Median overall survival (OS) was 20 months (95% confidence interval; 12.9–27.09 months), 3 and 4 years survivals were 27.9% and 20.9%, respectively. Median progression-free survival (PFS) was 9 months, 3 and 4 years PFSs were 20.1% and 16.1%. Myelosuppression was the most common toxicity. In 15 (19.2%) patients grade 2–3 lung toxicity and in seven (8.5%) patients' grade 2–3 dysphagia were reported.

Conclusion: Concurrent CRT with cisplatin and etoposide schedule is a well-tolerated regimen with acceptable toxicity profile and survival rates in patients with unresectable Stage IIIA/IIIB NSCLC. Median survival and OS results were consistent with the literature.

KEY WORDS: Concurrent chemoradiotherapy, nonsmall cell lung cancer, Stage III, survival

INTRODUCTION

Approximately, one of the three patients with nonsmall cell lung cancer (NSCLC) has unresectable locally advanced disease at diagnosis.[1] The prognosis of Stage IIIA and IIIB is poor and 5-year survival rates are 18% and 8%, respectively.[2] In the 1980s, radiotherapy (RT) alone achieved a median survival of <10 months and 3-year survival rates below 10% in these patients.[3-5] Combined modality therapy initially focused on a sequential approach with induction chemotherapy. Randomized phase III studies demonstrated an increased median survival from 10 months to approximately 13 months with two cycles of cisplatin-based chemotherapy administered before thoracic RT (TRT).[6-8] Moreover, chemotherapy and RT combinations have been recommended for the locally advanced disease.[7,9-11] These combinations have a theoretical advantage based on several interaction mechanisms between chemotherapy and RT. The CT minimizes the risk of distant metastasis, and radiation therapy provides loco-regional control.[12] And also chemotherapeutic drugs act as radiosensitizers by increasing the effect of RT.[13] Several randomized phase II and III trials have been shown that the concurrent approach results in a higher median survival of approximately 16–17 months at the cost of toxicity in particular esophagitis, is also increased (grade 3 or 4 in approximately 25%).[9-12,14-17]

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Several phase II and III studies of locally advanced NSCLC have analyzed different combinations of concurrent therapies.[18-25] Standard chemoradiotherapy (CRT) regimen, including radiation dose and schedule as well as selection and dosage of chemotherapeutic agents, has not been determined so far. Furthermore, the results obtained from clinical trials that held in the treatment of lung cancer patients are not always consistent with the results of real life data. Moreover, racial differences may prevent receiving similar results with the same treatment. The aim of this study was to assess the survival rates and safety of concurrent CRT with cisplatin (P) and etoposide (E) in Turkish patients with unresectable Stage III NSCLC.

PATIENTS AND METHODS

Patients' selection

This multicenter, retrospective cohort study was carried out at the two hospitals from two different provinces of Turkey. Between 2008 and 2012, 84 patients with unresectable Stage III NSCLC who met following criteria treated with concurrent CRT: Age 75 and younger; histological NSCLC diagnosis; measurable or assessable disease; no prior chemotherapy or RT; preregistration forced expiratory volume in 1 s (FEV_1) ≥1 L by spirometry; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 at baseline; unintended weight loss of <5% in the 3 months preceding study treatment; and adequate bone marrow, renal and hepatic functions. Patients were excluded if they had symptomatic peripheral neuropathy (must be ≤ grade 1) at baseline, malignant effusions (pleural or pericardial) or significant cardiac disease (uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction in prior year, or ventricular arrhythmias requiring medication). Unresectable Stage IIIA disease was defined by multiple and/or bulky N2 mediastinal lymph nodes on computed tomography (CT) scan or positron emission computed tomography (PET/CT) scans with [18F]-fluorodeoxyglucose (FDG). Stage IIIB patients must have had N3 or T4 status. N3 status must have been documented by the presence of a contralateral (to the primary tumor) mediastinal lymph node proven by biopsy or FDG PET. Patients with N3 disease due to supraclavicular lymph node involvement were not eligible.

Chemotherapy

All patient cohort received P 50 mg/m^2 intravenously (IV) on days 1, 8, 29, and 36 with E 50 mg/m^2 IV on days 1–5 and 29–33. Hydration and antiemetic regimen were used for all patients. Concurrent chemotherapy was applied on the 1st day of RT.

Radiotherapy

RT was delivered using conventional fractionation (1.8–2.0 Gy/day, 5 days/week) with a total dose of 58–66 Gy using 6–18 MV photon beams. All patients received three-dimensional conformal RT. The gross tumor volume (GTV) consisted of the primary tumor and the regional lymph nodes considered positive (SUVmax >2.5) on PET scan even if not involved by CT scan. Any intrathoracic lymph nodes with a diameter >10 mm in the short axis were included in GTV regardless of the PET scan. For GTV definition on CT, pulmonary window settings were used to contour the pulmonary tumor and hilum, and the predefined mediastinal window settings were used to contour the mediastinal lesions. Margins for GTV to clinical target volume (CTV) were 5–7 mm for squamous cell carcinoma (SCC) and 6–8 mm for other histologic types. To generate the planning target volume (PTV) 5–10 mm margin was added to the CTV to compensate setup errors and target motion. TRT was delivered to this volume at a daily dose of 1.8–2.0 Gy to a total dose of 45–46 Gy over 5 weeks. The 6th and 7th weeks of TRT were delivered to a smaller target volume encompassing the primary tumor and lymph nodes known to be involved with disease.

Dose volume histograms for the PTV, normal lung, esophagus, and heart have been calculated to gain full knowledge of the three-dimensional dose distribution. The total dose to the spinal cord was restricted to 48 Gy or less. For the heart, dose (D) mean and percentage volume receiving a dose of 40 Gy or more (V40) was calculated. For the lungs, percentage of lung volume receiving a dose of 20 Gy or more (V20) and mean lung dose (MLD) was calculated. MLD was defined as the average dose to total normal lung volume. For the esophagus, mean esophageal dose was calculated. Coverage of the CTV by the 95% isodose line was mandatory. PTV coverage with 95% isodose line was not achievable in some patients due to critical organ dose constraints. Treatment was delivered using a linear accelerator. TRT was interrupted for grade 3 or greater nonhematologic toxicity or grade 4 hematologic toxicity.

Patients' follow-up

Baseline history and physical examination, assessment of ECOG PS, FEV_1, CBC with platelet count (repeated on every weeks), serum chemistries (repeated on days 8, 29, and 36), and disease evaluation (CT of chest through the upper abdomen) were obtained in all patients. PET-CT scan and brain imaging (either CT or magnetic resonance imaging) were mandatory at baseline. Toxicities were weekly evaluated. Patients underwent response evaluation with CT of chest through the upper abdomen in the 4 weeks of completing treatment and follow-up continued every 3 months for the first 2 years, every 6 months for 3rd year, and yearly thereafter, with repeat CT of chest through the adrenals on each visit.

Response was assessed according to the response evaluation criteria in solid tumors criteria.[26] Toxicities were analyzed using the Common Toxicity Criteria for Adverse Events (version 3.0). Late-toxicity associated with TRT was graded according to radiation therapy oncology group late-toxicity criteria.[27]

Statistical analysis

This study was designed as a retrospective, multicenter cohort study. The primary endpoint of the study was the evaluation of overall survival (OS) and the secondary end points were

progression-free survival (PFS), response rate, and toxicity. OS and PFS were defined as the interval between the 1st day of CRT day and the date of death/last visit and date of progression respectively. Loco-regional relapse or distant progression was defined as, any type of local/regional or distant metastasis of the disease, Survival was analyzed by using the Kaplan–Meier method. SPSS (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago) was used for calculations.

RESULTS

Patients' characteristics

Eighty-four patients were evaluated. Two patients were excluded from the analysis due to migration of the initial stage on the final review. Characteristics of the patients are detailed in Table 1. Eighty-two patients (79 male/3 female; median age, 57 years; range 39–74 years) were analyzed in this study. The stages of the patients were Stage IIIA in 39 (47.5%) and IIIB in 43 (52.5%) patients. The histological diagnosis was SCC in 47 (57.3%), adenocarcinoma in 14 (17.1%), large cell carcinoma in 1 (1.2%) and unidentified in 20 (24.4%) of the patients.

Response and survival

Of 82 patients, 15 (18.2%) achieved a complete response, 31 (37.8%) achieved a partial response, 28 (34.2%) had stable disease, and 8 (9.8) had progressive disease. The median follow-up of alive patients was 40 months (range, 19–63 months). Sixty (73.2%) patients had died on last follow-up. The median OS was 20 months (12.9–27.09, 95% confidence interval [CI]), and 1-, 2-, 3- and 4-year OS rates were 67.1%, 41.5%, 27.9%, and 20.9%, respectively [Figure 1]. The median PFS time was 9.0 months (95% CI; 6.51–11.48 months), 1-, 2-, 3- and 4-year PFS rates were; 40.2%, 23.2%, 20.1%, 16.1%, respectively [Figure 2].

Toxicity profile

Concomitant treatment with E and P with TRT was generally well-tolerated. The most commonly occurring toxicity was myelosuppression [Table 2]. Major toxicity (grade 3 and greater, %): Neutropenia 45 (54.8%), leukopenia 34 (41.5%), thrombocytopenia 5 (6.1%), and febrile neutropenia 7 (8.5%). The majority of nonhematological toxicities were mild to moderate. A total of three (3.7%) patients presented with grade 3 fatigue, seven (8.5%) patients developed esophagitis, and one had a spontaneous pneumothorax. Late lung toxicity (grade 2–3) was detected in 15 (19.2%) and esophageal toxicity in two (2.5%) patients. Five patients had died at the

Table 1: Patient characteristics

	Number of patients (%)
Age, years	
Median (range)	57 (39-74)
Gender	
Male	79 (96.3)
Female	3 (3.7)
Performance status	
0	41 (50.0)
Weight loss	
None	62 (75.6)
Histology	
Squamous	47 (57.3)
Adenocarcinoma	14 (17.1)
Large cell	1 (1.2)
NSCLC	20 (24.4)
T and N substage	
T4 N0-1	19 (23.2)
T4 N2	29 (35.4)
T1-3 N2	19 (29.1)
T any N3	14 (17.1)
T3 N1	1 (1.2)
Stage	
IIIA	39 (47.5)
IIIB	43 (52.5)
Response	
CR	15 (18.2)
PR	31 (37.8)
SD	28 (34.2)
PD	8 (9.8)

NSCLC=Nonsmall cell lung cancer, CR=Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease

Table 2: Hematologic toxicity

	Neutropenia	Leukopenia	Anemia	Trombocytopenia
Grade 3-4 (%)	45 (54.8)	34 (41.5)	4 (4.9)	5 (6.1)

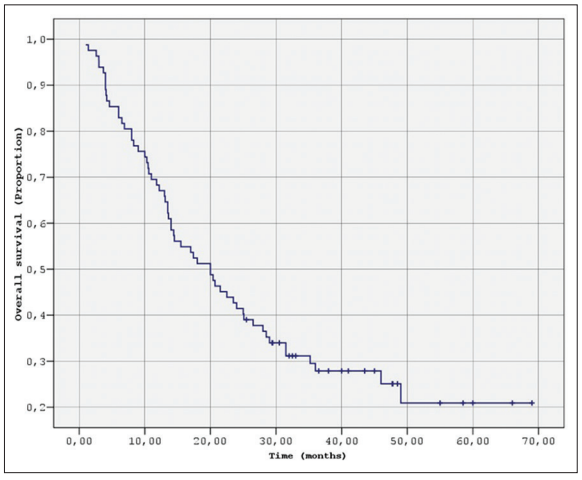

Figure 1: Overall survival

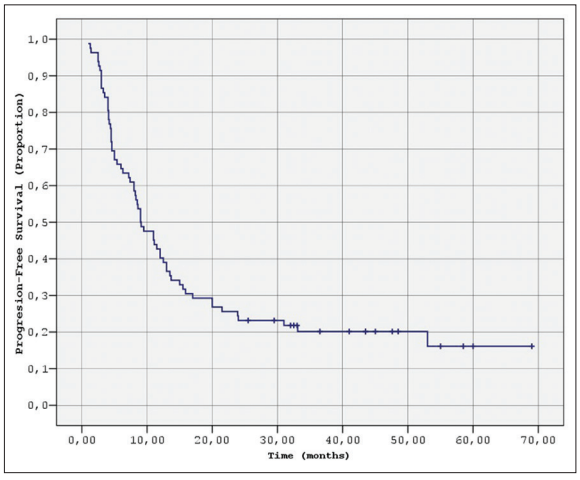

Figure 2: Progresion-free survival

times of analysis. The cause of death included neutropenic fever in two patients, massive hemoptysis in two patients and renal failure in one patient.

In analysis of the patterns of initial relapse, 41 (50.0%) patients out of 82 had documented relapse. Distant relapses identified in 19 (23.2%) patients, 37% of them relapsed in brain.

DISCUSSION

In this study, we evaluated the efficacy and toxicity of PE with concurrent TRT in patients with unresectable Stage III NSCLC. The median OS was 20 months and the median PFS was 9 months. The most commonly occurring toxicity was myelosuppression especially neutropenia with 54.8% of patients. Eight (9.8%) patients had progressive disease, and the most frequent site of distant metastases was the brain.

Concurrent CRT has been a standard treatment in patients with locally advanced NSCLC but a standard CRT protocol has not been established. Different cytotoxic drugs such as cisplatin, carboplatin, vinorelbine, taxanes, gemcitabine or etoposide and concurrent TRT have been used by different cancer centers. Several phase III studies were conducted with these drugs to examine the treatment response and toxicity.[17,24,28,29] The median OS ranges from 15 to 26 months, the response rates changes between 56% and 84% and the median PFS range was 8–13.4 months in prospective clinical trials using these regimens.[9,18,30,31] In this study, OS was 20 months and PFS was 9 months. Therefore, our data compare favorably with previous trials.

Several studies with different regimens examine optimal doses and drug toxicities and compare them with each other[10,25,32,33] Fournel *et al*. randomized 112 patients to receive sequential treatment with cisplatin and vinorelbin followed by TRT versus cisplatin and etoposide concurrent with TRT. Mean survival was 16.3 months with concurrent therapy.[10] Vokes *et al*. reported that three agents-cisplatin and gemcitabine, cisplatin and vinorelbine, and cisplatin and paclitaxel-combined with cisplatin and RT had similar activity, with response rates of 67–74% and median OS of 14.8–18.3 months.[25] The recent study has similar OS with ours for PE and demonstrated an improved survival in patients treated with concurrent RT over carboplatin and paclitaxel (20.2 months in PE vs. 13.5 months in PC).[33]

The main disadvantage of CRT is increased normal-tissue toxicity especially hematological, esophageal and pulmonary. In accordance with the recent studies[15,17,25,34,35] myelosuppression was the most frequent toxicity, in our study. Grade 3–4 hematological toxicities including neutropenia detected in 54.8% of patients, leukopenia 41.5%, thrombocytopenia 6.1% and anemia 4.%. Ishida *et al*. reported that 100% neutropenia in their study, these may be associated with the use of carboplatin in their study.[36] Wang *et al*. reported that the incidence of neutropenia was higher in PE arm than that in PC arm. Conversely, the incidence of grade 2 or greater pneumonitis was more frequent in PC than PE (48.5% vs. 25%).[33] In our study, we detected grade 2–3 pneumonitis in 19% of our patients.

In many studies, severe esophagitis has been reported and ranged from 3% to 18%. In a review of 12 different trials of PE, the mean rate for grade 3–4 esophagitis was 21.5%.[33] Nonhematological toxicities were milder in our study and no grade 4 esophagitis detected. In only 9 (11%) patients with grade 2–3 esophagitis established. Machtay *et al*. reported that PE when compared to PC regimen, had similar pathological response rates and survival, but PE regimen was associated with more grade 3 gastrointestinal toxicities (27% vs. 3%).[37] In the present study, relapses were identified in 41 (50%) patients, and 23.2% of these were a distant metastasis. Wang *et al*. also reported total failure, loco-regional relapses and distant metastases rates as 57.6%, 33.3%, and 33.3%, respectively.[33] The brain was the most common site consistent with the previous study.[38]

The management of these patients with Stage III NSCLC is one of the most controversial issues of the treatment and follow-up policy. A multidisciplinary team that includes pulmonologist, medical oncology, thoracic surgeon and the radiation oncologist is necessary for adequate management. Different regimens need to be studied to improve outcomes and select appropriate treatments for patients with Stage III NSCLC.

Due to the retrospective design of the current study, there are some important limitations. First, nodal staging was based in according to nodal FDG uptake with or without histologic evaluation. Second, all of the patients could not receive same thoracic radiation doses due to limiting organ toxicity in some patients and the different management programs of two different radiation oncology centers and various radiation oncologists. However, the relatively large and homogenous patient cohort and the long-term follow-up may overcome these limitations.

CONCLUSION

Our schedule for cisplatin and etoposide concurrent with TRT was well-tolerated and effective in unresectable Stage III NSCLC patients with limited toxic effects and good response rate and OS. For further studies, the search for more active regimens including cytotoxic and target specific agents and radiation dose adjustments are required for adequate management of patients with Stage III NSCLC.

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Conflicts of interest
There are no conflicts of interest.

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