Concomitant etoposide and cisplatin provided improved survival compared with docetaxel and cisplatin in patients with locally advanced non-small cell lung cancer treated with chemoradiotherapy

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Abstract

Presently, there is no consensus regarding which chemotherapy regimen is best to administer with radiotherapy in patients with locally advanced non-small-cell lung cancer (LA-NSCLC). Herein, our aim was to compare the outcome of patients treated with either etoposide–cisplatin (EP) or docetaxel–cisplatin (DP) in this curative setting.

Patients treated with either EP or DP and concurrent radiotherapy from 2004 to 2012 were identified and their detailed medical records and follow-up information were obtained for analysis in this retrospective study. Survival rates were compared using Cox proportional hazards regression models with adjustments for confounding parameters provided by propensity score methods.

A total of 105 patients were treated with concurrent chemoradiotherapy for LA-NSCLC (stage IIB-IIIA-IIIB). The median ages were 54 years (range, 32–70 years) and 55 years (range, 37–73 years) in the EP (n = 50) and DP (n = 55) groups, respectively. The median follow-up time was 27 months (range, 1–132 months) in the EP group and 19 months (range, 1–96 months) in DP group. There was no significant difference in baseline clinicopathologic features including age, sex, performance status, histologic subtype, and clinical TNM stages between groups. In the univariate analysis, the median overall survival of patients treated with EP was higher than that of patients treated with DP (41 vs. 20 months, $P = 0.003$). Multivariate analysis further revealed a survival advantage with EP compared with DP (hazard ratio [HR], 0.46; 95% confidence interval: 0.25–0.83; $P = 0.009$). The toxicity profile of the 2 treatment groups was similar except that pulmonary toxicity was higher in the DP group (grade 3–4: 0% vs. 6%, $P = 0.024$).

Concurrent chemoradiotherapy with EP may provide more favorable outcomes than DP and with an acceptable safety profile.

Abbreviations: DP = docetaxel–cisplatin, EP = etoposide–cisplatin, LA-NSCLC = locally advanced non-small-cell lung cancer, PC = carboplatin/paclitaxel, PV = cisplatin/vinblastin.

Keywords: concomitant chemoradiotherapy, docetaxel-cisplatin, etoposide-cisplatin, locally-advanced NSCLC, lung cancer

1. Introduction

The primary cause of cancer death is lung cancer. The estimated new cases and deaths because of lung cancer in the United States in 2015 were 221,200 and 158,040, respectively,[1] whereas the 5-year survival rate for patients with lung cancer is 17.4%.[2] Including small-cell lung carcinoma, only 37% of lung cancer is diagnosed while it is still confined to the primary site or spread to regional lymph nodes or directly surrounding tissues; 5-year survival rates for patients with localized and regional tumors are 54% and 26.5%, respectively.[2] It is essential to manage the disease locoregionally to increase the survival rates of patients who have locally advanced disease (LA-NSCLC) with no distant metastasis.

Although the management of localized or metastatic disease is well established, there are major ongoing controversies for locally advanced disease. Although randomized trials failed to show any survival benefit provided by surgery in stage IIIA disease, surgery may be still an option for patients with single N2 node (<3 cm).[3–5] For the remaining patients, neoadjuvant chemoradiotherapy (CRT) or chemotherapy (CT) is recommended, whereas in cases with multiple >3-cm pathologically proven malignant lymph nodes, definitive CRT is more convenient.[6] Furthermore, a recently published meta-analysis that included 7 trials with 1049 patients revealed that neoadjuvant CT/CRT followed by surgery was not superior to neoadjuvant CT/CRT followed by radical RT in patients with stage IIIA disease.[7]

The combined CRT was shown to be superior to RT alone in unresectable stage IIIA-IIIB NSCLC in several studies.[8,9] In addition, concurrent CRT is more effective than sequential CRT at the expense of an increase in grade 3–4 esophagitis.[10,11] However, one of the main debates centers on which CT regimen is more efficient with concomitant CRT. To date, the suggested CT regimens for all histologies include cisplatin/etoposide (EP), cisplatin/vinblastine (PV), and carboplatin/paclitaxel (PC), and a platin combination with pemetrexed may be used for patients with nonsquamous NSCLC.[10,12–18] Nevertheless, there is no current consensus on which CT regimen is the best to administer concomitantly with RT in patients with LA-NSCLC.[19]

Randomized trials regarding this subject mainly included PE or PV regimens.[19] Several recent studies compared PE with PC in terms of efficiency and produced conflicting results.[14,20–22] However, docetaxel is a third-generation CT agent and its effectiveness has been demonstrated in many studies indicating that the docetaxel-cisplatin (DP) regimen was equal or superior to a PV combination.[23–26] In addition, docetaxel proved its superiority to vinca-alkaloids in combinations in both metastatic and LA-NSCLC.[23,27] Furthermore, a meta-analysis revealed that docetaxel-based CT provided longer survival than vinca alkaloid-containing regimens.[28]

The phase II Southwest Oncology Group S9504 trial, which added docetaxel consolidation to concomitant EP, notified a median survival of 26 months.[29] However, no studies have compared EP regimen with DP in LA-NSCLC. The only trial that compared EP with a cisplatin-taxane combination including paclitaxel but not docetaxel was conducted by the Eastern Cooperative Oncology Group. Their study comprised 599 patients with stage IIIB-IV NSCLC who received either EP or a cisplatin-paclitaxel regimen; the authors reported a survival benefit in favor of paclitaxel.[30] Nevertheless, the efficacy of DP over EP still remains unknown. Thus, we conducted the present study to address the question as to whether DP is superior to EP in patients with LA-NSCLC who are concurrently treated with CRT in terms of survival and safety.

2. Material and methods

2.1. Study design and eligibility criteria

The medical records of approximately 10,000 patients with lung cancer who were referred to Istanbul University Institute of Oncology from 2004 to 2012 were evaluated. Among them, patients with stage IIB, IIIA, or IIIB histopathologically confirmed NSCLC whose medical records were available in detail were included in the study. The 10th edition of American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) systems was used while staging according to radiologic and pathologic findings. Adverse effects were evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.

The treatment decision was taken by a multidisciplinary team that included a medical oncologist, radiation oncologist, pathologist, chest disease specialist, thoracic surgeon, radiologist, and a nuclear medicine specialist. Patients who were inoperable were treated with radical CRT, CRT followed by consolidation CT, or induction CT followed by CRT. Patients whose tumors were too large for radiotherapy (RT) received induction CT. All patients were evaluated for surgery eligibility at each step. Patients who became operable underwent surgery including lobectomy, bilobectomy, or pneumonectomy.

The pretreatment evaluation included a detailed clinical history and physical examination with a series of biochemistry tests and complete blood cell counts. Selection for treatment required an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2, and appropriate bone marrow (absolute neutrophil count >1500 cells/μL, and platelet count >100,000 cells/μL), and cardiac, renal, and hepatic function.

Patients were treated with either etoposide (50 mg/m^2 on days 1–5 and 29–33) and cisplatin (50 mg/m^2 on days 1,8,29, and 36) (EP) or 6 cycles of weekly DP (each 20 mg/m^2) concurrently with radiotherapy up to a 60 Gy. Linear accelerators (Simens/Oncor Impression, Varian DBX 600C and Varian Trilogy-Rapid arc) with a 6 to 15 MV photon beam were used for radiotherapy. All patients underwent 3-dimensional treatment planning using either CMS-XIO (CMS Inc, St Louis, MO) or Varian Eclipse TPS station version 8.9 (Varian Medical Systems, Palo Alto, CA) treatment planning systems. Treatment planning was based on CT scans with 5-mm section thickness and 5-mm intervals obtained in a treatment position. Customized devices were used to immobilize the patients. Radiotherapy was administered with an angled field technique to include the entire planning tumor volume (PTV) in the isodose 95% area. Gross tumor volume (GTV) was defined as tumor extension and metastatic lymph nodes. The clinical target volume (CTV) was GTV plus a 1-cm margin. PTV consisted of CTV plus 1 cm to the superior-inferior direction and 0.5 cm to the anterior-posterior and left-right directions. The median total dose was 60 Gy/2 Gy/d.

All patients had pretreatment imaging of primary tumors with magnetic resonance imaging (MRI) or computed tomography. For patients with evaluable imaging studies before and after treatment, radiologic response was recorded according to the Response Evaluation Criteria in Solid Tumors (RECIST) or PET Response Criteria in Solid Tumors (PERCIST), and classified as follows: complete response (CR), partial response (PR), stable disease (SD), or progressive disease. Disease follow-up programs included physical examination, laboratory tests, and computed tomography scan or MRI depending on which imaging methods were indicated, and performed every 3 months for the first 2 years, every 6 months for the following 3 years, and annually thereafter with no anticancer treatment.

Baseline characteristics of patients and diseases including age, sex, weight loss, ECOG performance status, histologic type, clinical T and N stages, as well as treatment type, CT regimen, operability, progression during follow-up, metastasis, hematologic and nonhematologic adverse effects of treatment were obtained retrospectively in detail for all patients from their medical records.

All procedures performed in studies involving human participants were in accordance with the ethics standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethics standards. Formal consent is not required for this type of study.

2.2. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) for Windows version 16.0 (SPSS Inc., Chicago, IL) was used for data analysis. Continuous variables were categorized using median values as cutoff points. Student t test was used to compare continuous variables between the groups, and χ^2 and/or Kruskal–Wallis tests were performed for the comparison of categorical variables.

Overall survival (OS) was calculated from the date of first admission to disease-related death or date of last contact with the patient or any family member. Progression-free survival (PFS) was calculated from the date of admission to the date of first radiologic progression. Kaplan–Meier analysis was performed

Table 1

Comparison of clinical and pathological variables of non-small cell lung cancer patients treated with concomitant chemoradiotherapy either with etoposide and cisplatin or docetaxel and cisplatin.

Variable	Etoposide and cisplatin		Docetaxel and cisplatin		P
	N	%	N	%	
Age					
Median	54		55		0.41
Min-max	32–70		37–73		
Sex					
Male	46	92%	53	%96	0.33
Female	4	8%	2	%4	
Weight loss					
Yes	15	30%	10	19%	0.20
No	35	70%	42	81%	
ECOG PS					
0	21	42%	30	55%	0.19
1+	29	58%	25	45%	
Histological type					
Squamous	24	48%	25	46%	0.38
Non-squamous	16	32%	13	24%	
NSCLC-NOS*	10	20%	17	30%	
Lung					
Right	29	58%	33	64%	0.35
Left	21	42%	19	36%	
Clinical T stage					
T1–3	36	72%	31	57%	0.12
T4	14	28%	23	43%	
Clinical N stage					
N0	8	16%	12	19%	0.59
N1	2	4%	2	4%	
N2	30	60%	34	62%	
N3	10	20%	6	15%	
Stage					
IIIB	29	58%	32	58%	0.96
IIB-IIIA	21	42%	23	42%	
Surgery					
Yes	12	24%	9	16%	0.30
No	37	76%	46	84%	
Radiation dose					
Mean (Gy)	59		54		0.028
Median ± SD (Gy)	60 ± 6.8		60 ± 11.2		
Radiation dose					
<60 Gy	38	76%	39	76%	0.95
≥ 60 Gy	12	24%	12	24%	
Induction or consolidation therapy					
Yes	17	34%	46	84%	<0.001
No	33	66%	9	16%	
Treatment response					
Responders (PR + CR)	39	80%	43	80%	0.99
Nonresponders (SD + PD)	10	20%	11	20%	

CR = complete response, NSCLC = non-small-cell lung cancer, PD = progressive disease, PR = partial response, SD = standard deviation.

for the estimation of survival distribution and differences in PFS and OS. The log-rank test was used to assess statistical significance in univariate comparisons. To adjust for potential covariate effects, Cox proportional hazards regression was used as the modeling paradigm. Multivariate analysis was conducted using Cox regression modeling. All statistical tests were 2-sided and a P value ≤0.05 was considered statistically significant.

3. Results

In total, 50 patients (median age 54 years; range, 32–70 years) who were given concurrent EP, and 55 patients (median age 55 years; range, 37–73 years) who were given concurrent DP were enrolled in

the analyses. There was no statistically significant difference in baseline clinicopathologic features including age ($P = 0.41$), sex ($P = 0.33$), weight loss ($P = 0.20$), ECOG performance status ($P = 0.19$), histologic type ($P = 0.38$), lung site ($P = 0.35$), clinical T and N stage ($P = 0.59$ and $P = 0.12$, respectively), disease stage ($P = 0.96$), surgery ($P = 0.30$), radiation dose (<60 vs. ≥60 Gy) ($P = 0.95$), and treatment response ($P = 0.99$) between the groups. However, the mean radiation dose was higher in the EP group compared with the DP group (59 vs. 54 Gy; $P = 0.02$). In addition, induction or consolidation CT administration was more common in the DP group than in the EP group (84% vs. 34%; $P < 0.001$). The comparison of baseline characteristics of patients and treatment details of the 2 groups is shown in Table 1.

Table 2

Univariate analysis of progression free survival of patients.

Variable	No. of events	Median PFS, mo	Univariate analysis 95% CI	P
Concurrent chemotherapy				
E+P	30/49	19	3.75–34.24	0.021
D+P	44/54	10	5.48–12.51	
Age, y				
≤55	40/58	15	8.39–21.60	0.41
>55	34/45	13	6.44–19.55	
Sex				
Male	70/97	13	6.71–19.29	0.73
Female	4/6	13	0–33.164	
Weight loss				
Yes	17/25	9	5.32–12.67	0.84
No	55/76	16	9.93–22.06	
ECOG PS				
0	32/49	11	8.05–13.94	0.38
1+	42/54	18	10.818–25.18	
Histological type				
Squamous	29/48	19	0–42.35	
Non-squamous	25/29	11	6.78–15.21	0.11
NSCLC-NOS	20/26	9	4–13.99	
Lung				
Right	42/61	18	6.10–29.89	0.12
Left	30/40	10	7.41–12.59	
Surgery				
No	6/81	13	6.20–19.79	0.09
Yes	13/21	35	0–80	
Clinical T stage				
T1–3	44/65	16	8.26–23.73	0.11
T4	30/37	10	5.11–14.88	
Clinical N stage				
N0	13/19	6	1.73–10.26	
N1	2/4	35		0.33
N2	45/63	18	12.41–23.58	
N3	14/16	9	5.08–12.92	
Stage				
IIIB	39/59	15	7.47–22.52	0.29
IIB-IIIA	34/43	13	4.38–21.66	
Treatment response				
Yes	52/80	22	11.05–32.94	<0.001
No	21/21	6	4.22–7.78	
Induction or consolidation therapy				
Yes	47/61	13	8.76–17.23	0.26
No	27/42	19	4.66–33.33	
Radiation dose				
<60 Gy	21/29	11	0.62–21.37	0.55
≥60 Gy	70/99	16	9.57–22.43	

CI = confidence interval, NSCLC = non-small-cell lung cancer, PFS = progression-free survival.

The median (min–max) follow-up time of patients was 27 months (range, 1–132 months) in the EP group and 19 months (range, 1–96 months) in the DP group. In the univariate analysis, median PFS of patients treated with EP was found higher than that of patients treated with DP (PFS = 19 months, 95% confidence interval [CI] 4–34 vs. 10 months 95% CI 5–12; $P = 0.02$) (Table 2), as well as in patients with treatment response (PFS = 22 months, 95% CI 11–33 vs. 6 months 95% CI 4–8; $P < 0.001$).

In the univariate analysis, the median OS of patients treated with EP was found higher than that of patients treated with DP (OS = 41 months; 95% CI 26–56 vs. 20 months, 95% CI 14–26; $P = 0.003$) (Fig. 1). Furthermore, right-sided tumor (OS = 30 months; 95% CI 16–44 vs. 19 months, 95% CI 12–26;
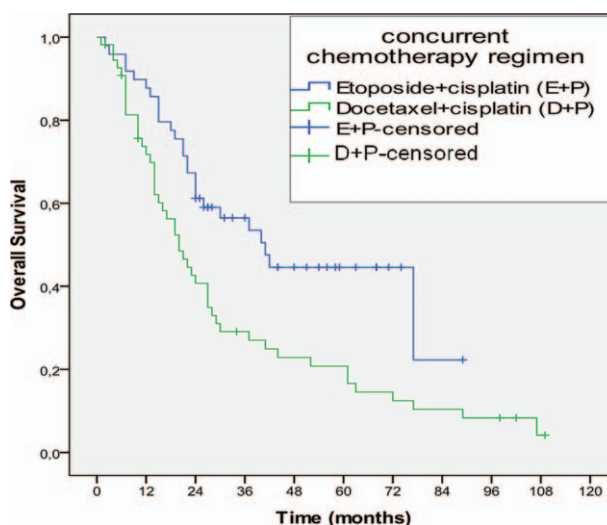
Figure 1. The comparison of overall survival between etoposide and cisplatin and docetaxel and cisplatin groups.

$P = 0.029$), surgery performance (OS = 52 months; 95% CI 13–92] vs. 23 months, 95% CI 20–26]; $P = 0.023$), and treatment response (OS = 40 months; 95% CI 29–83 vs. 17 months, 95% CI 17–2; $P < 0.001$) were detected associated with longer OS time in the univariate analysis. There was no statistical significance in terms of age ($P = 0.07$), sex ($P = 0.98$), weight loss ($P = 0.68$), ECOG performance status ($P = 0.51$), histologic type ($P = 0.63$), clinical T and N stage ($P = 0.33$ and $P = 0.32$, respectively), disease stage ($P = 0.45$), induction or consolidation therapy ($P = 0.06$), and radiation dose ($P = 0.12$) significance (Table 3).

Multivariate analysis further revealed survival advantage with EP compared with DP (hazard ratio [HR] = 0.46; 95% CI 0.25–0.83; $P = 0.009$). Significant variables were stratified with respect to potential confounding factors such as age, weight loss, T stage, histology, and stage of nodal involvement. In addition, both right-sided tumors (HR = 0.58; 95% CI 0.35–0.98; $P = 0.041$) and treatment response (HR = 0.26; 95% CI 0.15–0.48; $P < 0.001$) were found correlated with better survival time. Neither surgery (HR = 0.65; 95% CI 0.32–1.28; $P = 0.22$) nor induction or consolidation therapy was associated with survival in the multivariate analysis (HR = 0.84; 95% CI 0.54–1.65; $P = 0.94$). The results of multivariate analysis are shown in Table 4.

The toxicity profile of 2 treatment groups including anemia ($P = 0.91$), thrombocytopenia ($P = 0.47$), nausea/vomiting ($P = 0.69$), esophagitis ($P = 0.69$), neurotoxicity ($P = 0.20$), nephrotoxicity ($P = 0.38$), hepatotoxicity ($P = 0.37$), and diarrhea ($P = 0.76$) was found similar except that pulmonary (grade 3–4: 0% vs. 6%, $P = 0.02$) and skin toxicities (grade 1–2: 4% vs. 24%, $P = 0.01$) were higher in the DP group compared with EP. Although neutropenia incidence was slightly higher in the EP group than with DP (grade 3, 8% vs. 0%, $P = 0.055$), the infection rate was similar between the 2 groups (grade 3–4, 0% vs. 6%, $P = 0.08$). Detailed toxicity comparisons of the 2 groups are represented in Table 5.

4. Discussion

There are several CT combinations choices to consider for concomitant treatment, among which the most accepted and

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Table 3

Univariate analysis of overall survival of patients.

Variable	No. of events/total N	Median survival, mo	Univariate analysis 95% CI	P
Concurrent chemotherapy				
E + P	26/50	41	26–56	0.003
D + P	48/55	20	14–26	
Age, y				
≤55	36/58	37	14–38	0.07
>55	38/46	25	19–29	
Sex				
Male	70/99	26	20–33	0.98
Female	4/6	22	0.88–43	
Weight loss				
Yes	16/25	28	11–45	0.68
No	55/76	26	21–31	
ECOG PS				
0	39/50	27	22–31	0.51
1+	39/55	24	14–34	
Histological type				
Squamous	32/49	40	15–67	0.63
Non-squamous	22/29	28	25–31	
NSCLC-NOS	20/26	22	18–26	
Lung				
Right	40/61	30	16–44	0.029
Left	31/40	19	12–26	
Surgery				
No	63/82	23	20–26	0.023
Yes	11/21	52	13–92	
Clinical T stage				
T1–3	46/66	27	21–33	0.33
T4	27/37	22	15–29	
Clinical N stage				
N0	14/20	27	14–40	0.32
N1	1/4	–		
N2	44/63	27	21–33	
N3	14/16	21	18–24	
Stage				
IIIB	40/59	28	24–32	0.45
IIB-IIIA	32/43	23	20–26	
Treatment response				
Yes	51/81	40	29–83	<0.001
No	21/21	17	17–21	
Induction or consolidation therapy				
Yes	50/62	23	18–26	0.06
No	24/42	41	23–59	
Radiation dose				
<60 Gy	55/76	24	18–30	0.12
≥60 Gy	15/24	63	1–129	

CI = confidence interval, NSCLC = non-small-cell lung cancer, PFS = progression-free survival.

Table 4

Multivariate analysis of overall survival of patients.

Variable	No. of events/total N	Median survival, mo	Multivariate Cox analysis HR	95% CI	P
Concurrent chemotherapy					
E + P	26/50	41	0.45	0.25–0.83	0.009
D + P	48/55	20			
Lung					
Right	40/61	30	0.58	0.35–0.98	0.041
Left	31/40	19			
Surgery					
Yes	11/21	52	0.65	0.32–1.28	0.22
No	63/82	23			
Treatment response					
Yes	44/72	41	0.26	0.15–0.48	<0.001
No	25/27	19			
Induction or consolidation therapy					
Yes	50/62	23	0.84	0.54–1.65	0.94
No	24/42	41			

CI = confidence interval, HR = hazard ratio.

regimen based on the data of the large database of the Veterans Health Administration. However, the results of the only randomized trial that compared EP with CP showed that EP provided higher survival time and less pulmonary but higher hematologic toxicity than EP, which is fully compatible with our results.[32]

The conflicting results of these 2 studies gave rise to the following question in our minds: "Was the superiority of the EP regimen over CP combination caused by the superiority of cisplatin over carboplatin in the study of Wang et al?" Because the Lung Adjuvant Cisplatin Evaluation meta-analysis demonstrated that carboplatin was not as efficient as cisplatin at eliminating micrometastasis in the adjuvant setting of stage II and III NSCLC.[33] Accordingly, we decided to compare 2 cisplatin-containing regimens with standard etoposide or docetaxel, and our results indicated that EP was still superior to DP, which verified the findings of Wang et al.[20]

Concurrent chemoradiotherapy with EP may provide more favorable outcomes than that of DP with a better safety profile. This finding is similar to those previously reported in the literature.[20] The median OS and PFS achieved with EP in our group of patients were 40 months and 19 months, respectively, which were considerably higher compared without comes reported in the INT 139-patient trial (23.6 months and 12.8 months, respectively) that used the same CT protocol.[3] Furthermore, both CT regimens resulted in median OS rates that were better than expected on the basis of data from previously reported studies in patients with stage III NSCLC.[29] The reason for this inconsistency may be related to the fact that patients enrolled in our study with mediastinal nodal (N2) or N3 involvement were judged to be fit for rigorous therapy. Additionally, pathologic confirmation of mediastinal staging could not be performed to all patients; this may clinically result in upstaging of patients whose disease stages may actually be earlier.

Pulmonary toxicity occurs as a frequent complication of lung cancer therapy with concurrent chemoradiation.[34] It is estimated that the frequency of this complication is between 10% and 30% depending on factors such as volume of the irradiated area, irradiation technique, the type of CT agents given, as well as the previous pulmonary comorbidities of the patient.[35] Taxanes are well known antineoplastics that have the potential to induce pulmonary injury through a variety of

commonly used is EP.[19] The other frequent options are combinations of platin with taxanes and vinorelbine; however, the best remains to be elucidated because of a lack of large, randomized trials.[19] Nonetheless, there is some evidence for which combination might be more effective. For instance, in a meta-analysis by Shen et al[31] that included 9 randomized controlled trials with 1741 patients, the DP combination was revealed to be superior to cisplatin and vinorelbine in advanced NSCLC concerning response to treatment and survival rates, and with a better safety profile. The current controversies continue as to whether standard EP regimen is superior to a platin plus taxane combination. The most commonly preferred platin–taxane regimen in North America and some parts of Europe is CP.[19] Santana-Davila et al[31] reported that CP was as effective as EP

Table 5

Safety profile of overall treatment procedure.

Toxicity	E+P		D+P		
	N	%	N	%	P
Anemia					
Grade 1	14	29	13	25	0.91
Grade 2	6	13	7	14	
Grade 3–4	0	0	0	0	
Neutropenia					
Grade 1	2	4	0	0	0.055
Grade 2	0	0	1	2	
Grade 3	4	8	0	0	
Thrombocytopenia					
Grade 1	2	4	1	2	0.47
Grade 3	1	2	0	0	
Nausea/vomiting					
Grade 1	6	12	7	14	0.69
Grade 2	7	15	5	10	
Grade 3	0	0	1	2	
Esophagitis					
Grade 1	7	15	11	22	0.69
Grade 2	14	29	17	33	
Grade 3	3	6	3	6	
Skin					
Grade 1	2	4	8	16	0.017
Grade 2	0	0	4	8	
Pulmonary					
Grade 1	1	2	9	18	0.024
Grade 2	0	0	1	2	
Grade 3–4	0	0	3	6	
Neurotoxicity					
Grade 1	1	2	5	10	0.20
Grade 2	1	2	0	0	
Grade 3	1	2	0	0	
Nephrotoxicity					
Grade 1	1	2	3	6	0.38
Grade 2	0	0	1	2	
Hepatotoxicity					
Grade 1	0	0	1	2	0.37
Diarrhea					
Grade 1	2	4	3	7	0.76
Grade 3	2	4	1	2	
Infection					
Grade 1	0	0	4	8	0.08
Grade 2	5	10	1	2	
Grade 3	0	0	2	4	
Grade 4	0	0	1	2	

mechanisms.[36] Among the third-generation agents used with radiation in current practice, docetaxel might be the most toxic.[36] This drug has resulted in a relatively high rate of serious (NCI-CTC grade 3) pneumonitis, reported to occur in as many as 47% of patients treated concurrently with radiotherapy.[35] In our study, the frequency (6%) of severe pulmonary toxicity seen with weekly docetaxel and cisplatin was lower than the previously reported data, which may be because of careful patient selection, meticulous RT volume planning, as well as prompt supportive treatment initiated at the first sign of pneumonitis.

Although most adverse effects were comparable between the 2 groups, grade 3 neutropenia was more common among patients who received EP concomitantly, which is similar to previous reports.[22] The incidence of severe neutropenia and thrombocytopenia was considerably lower in our study (12% and 0%,

respectively) compared with other studies including PE regimen (39% vs. 10%).[22] Variations in terms of efficiency and toxicity have been reported between different nations receiving the same CT regimens.[37] These differences mainly emerge from ethnic instabilities in single-nucleotide polymorphism distributions that affect CT transport and metabolism.[38] It is well-established that the pharmocogenomic variability in genes may result in inter-racial and individual disparity concerning toxicity and outcomes.[39] Our population comprised only Turkish patients; however, no pharmocogenomic study has investigated the distribution of gene polymorphisms in the Turkish population. Additionally, severe skin toxicity was not observed in any of the treatment arms; however, grade 2 skin toxicity was more frequent in patients who received DP (12% vs. 0%, $P=0.017$). Increased cutaneous toxicity with docetaxel has been reported, especially in patients with breast cancer.[32,40]

The present study is a nonrandomized, retrospective study, which caused some limitations. First, the population of our study mainly consisted of men (>90%). The incidence of NSCLC has increased recently, and the rate of women diagnosed with NSCLC is about 35% to 40%.[19] Second, >45% of patients had squamous cell lung cancer in the present study, whereas adenocarcinoma histology is the most common subtype among patients with LA-NSCLC referred to oncology centers.[19] Last, the number of patients is relatively small.

5. Conclusions

In conclusion, we reported the toxicities and clinical outcomes of patients with unresectable stage III NSCLC treated with concurrent thoracic RT with either PE or DP. Given that PE provided better outcomes with less pulmonary but greater hematologic toxicity, we believe that PE might be more appropriate to administer concomitantly with close monitoring for neutropenia. Still, the results of our study warrant further investigation in randomized studies to make a final decision.

Acknowledgments

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