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ORIGINAL ARTICLE

Comparison of two different carboplatin and weekly paclitaxel schedule in elderly advanced non-small cell lung cancer patients

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Abstract

Purpose In this study our aim was to compare efficacy and toxicity profiles of two different schedule of carboplatin-paclitaxel regimen in elderly advanced non-small cell lung cancer (NSCLC) patients.

Methods Data from the charts of 59 elderly patients with metastatic NSCLC, treated with weekly paclitaxel combined with two different schedule of carboplatin were collected retrospectively from three medical oncology centers in Turkey between September 2002 to March 2018. No prior systemic therapy or radiotherapy was allowed. Brain metastases were not considered as exclusion criteria unless symptomatic. Patients were analyzed in two treatment groups; CP3 (who received 3 weekly carboplatin and weekly paclitaxel), and CP1 (weekly carboplatin and weekly paclitaxel). Overall survival (OS) was the primary endpoint of the study. Secondary end points were as follows: progression free survival (PFS), response rates (RR), grade 3–4 toxicities, skipped cycles, dose reductions, and treatment discontinuation rates.

Results Twenty-four patients received 3 weekly carboplatin and weekly paclitaxel schedule (CP3) while weekly carboplatin and weekly paclitaxel schedule (CP1) was performed in 35 patients. CP3 had a median OS of 14 months whereas CP1 had 9 months of median OS ($p=0.084$). Both treatments (CP3 vs CP1) had similar median PFS (7 months vs 4 months, $p=0.109$) and objective RR (20.9% vs 29.4%, $p=0.465$). There was an increased incidence of grade 3–4 anemia and grade 3–4 neutropenia in CP3 compared to CP1 ($p=0.003$ in both), but no major differences in febrile neutropenia and infection toxicity profiles ($p=0.289$ and $p=0.770$, respectively). Weekly schedule (CP1) had a tendency of increased grade 3–4 neurotoxicity (33.3% vs 42.9%, $p=0.461$).

Conclusion Weekly carboplatin and paclitaxel might be more tolerable and is as effective as 3 weekly carboplatin and weekly paclitaxel schedule in metastatic elderly NSCLC patients.

Keywords NSCLC · Elderly · Carboplatin · Paclitaxel

Abbreviations

AUC	Area under curve
CI	Confidence interval
CP3	3 weekly carboplatin with weekly paclitaxel
CP1	Weekly carboplatin with weekly paclitaxel
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
NSCLC	Non-small cell lung cancer
FEN	Febrile neutropenia
mo	Month
NA	Not available
NS	Not significant
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD-L1	Programmed death ligand 1
PFS	Progression free survival
wk	Week

Introduction

Non-small cell lung cancer (NSCLC) is frequently diagnosed in elders and majority of these patients are above the age of 65 years with median age at diagnosis is 70 years in SEER data [1]. Mean age for NSCLC was 61.5 ± 10 years in Turkish cancer epidemiologic study [2]. In advanced NSCLC with

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negative molecular and immunological markers (negative for EGFR sensitizing mutation, ALK or ROS-1 rearrangement, and PDL-1 expression), platinum based chemotherapy combinations are considered as the gold standard first line treatment [3]. Prior clinical practice guidelines suggested monotherapy or best supportive care in elderly patients and senior patients, especially older than 70 years old, were not included in clinical trials until Italian ELVIS study [4]. Treatment of elderly patients with advanced NSCLC started to change in 2001 when single agent vinorelbine significantly prolonged survival [4]. Subsequent researches investigated doublet combination treatments which revealed superior clinical responses [5] and survival rates [6, 7]. Doublet chemotherapy regimens, either platinum based or non-platinum based showed no survival or clinical response difference [8, 9] but nowadays platinum-based regimens are the most preferred treatments. Minimum adverse events with the best efficacy is important in the treatment of elderly patients with multiple comorbidities [10] and evidence based treatment is not definite.

Aging is accompanied by gradual loss of renal functions [11]. Because of the reduced renal clearance of drugs, carboplatin based regimens are considered more reliable and legitimate treatment approach in this population [10]. Herein carboplatin and paclitaxel regimens are frequently preferred treatments in elderly advanced NSCLC patients. In recent studies carboplatin–paclitaxel regimens were studied in different schedules and intervals. Ramalingam and colleagues compared standard 3-weekly regimen of carboplatin–paclitaxel with 4-weekly paclitaxel (days 1, 8, 15) and carboplatin (day 1), and reported no difference in efficacy but less neurotoxicity with weekly schedule [12]. In the sub analysis of this trial, similar efficiencies were observed in three different weekly paclitaxel/carboplatin schedules in both groups aged ≥ 70 years and < 70 years [13]. Comparable efficacy was shown in various other studies [14, 15] and weekly paclitaxel in combination with carboplatin is accepted as a good first-line treatment alternative. Optimal less toxic carboplatin–paclitaxel schedule for elderly advanced NSCLC patients should be elucidated. In this study our aim was to compare efficacy and toxicity profiles of two different widely used weekly paclitaxel schedule with different carboplatin intervals in advanced NSCLC patients 65 years- and older. From this point of view, this real-life data might help to direct us for the best treatment schedule in this group of patients.

Materials and methods

Study design and patients

Data from the charts of 59 patients treated between September 2002 to March 2018 were collected retrospectively from three medical oncology centers in Turkey (Marmara University Pendik Education and Research Hospital in Istanbul; Antalya Education and Research Hospital in Antalya; and Hacettepe University Hospital in Ankara). Patients with histologically or cytologically confirmed metastatic NSCLC, ages 65 years- or older, and treated with weekly paclitaxel combined with 2 different schedule of carboplatin were included in this study. No prior systemic therapy or radiotherapy was allowed. Brain metastases were not considered as exclusion criteria unless symptomatic. Patients were analyzed in two treatment groups; CP3 (who received 3 weekly carboplatin and weekly paclitaxel), and CP1 (weekly carboplatin and weekly paclitaxel). Study design and treatment schedules are shown in Fig. 1.

Overall survival (OS) was the primary endpoint of the study. OS was defined as the time from diagnosis to death. Secondary end points were as follows: progression free survival (PFS), response rates (RR), grade 3–4 toxicities, skipped cycles, dose reductions, and treatment discontinuation rates. PFS was defined as the time from first treatment date to documented progression or death. The study protocol was approved by the local ethics committee.

Assessment of response

Radiological response was assessed on every three cycles or in case of a clinical progression finding by using Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). All patients had baseline computed tomography (CT) or positron emission tomography (PET–CT).

Assessment of toxicity

Toxicity was assessed on every cycle. For toxicity analysis, the worst data for each patient in all cycles of chemotherapy were used. Toxic effects were graded according to Common Terminology Criteria for adverse Events (CTCAE) which was used at the time of treatment [16].

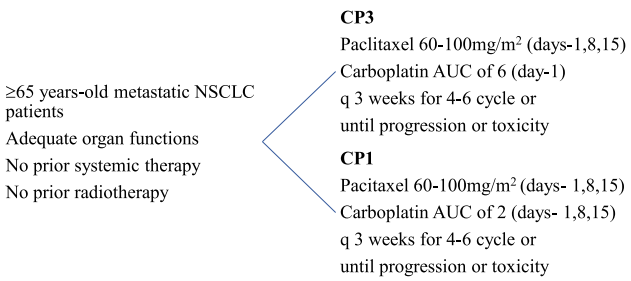


Fig. 1 Study design and treatment schedule diagram

Statistical methods

Statistical analysis was made using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). Normality assumptions were controlled by the Shapiro–Wilk test. Descriptive analyses were presented using median (min–max) or *n* (%), where appropriate. Categorical data were analyzed by Pearson Chi square or Fisher's exact test. Comparisons of continuous variables between the two groups were performed using the nonparametric Mann–Whitney *U* test. The Kaplan–Meier method and log-rank tests were used in the analysis. A univariate Cox proportional hazards regression model was used to identify prognostic factors. Hazard ratio (HR), with corresponding 95% confidence intervals (95% CIs), was reported. A *p* value of less than 0.05 was considered statistically significant.

Results

Patient demographics

The baseline characteristic of 59 patients are outlined in Table 1. Age, gender, ECOG performance status (PS), histopathological subtypes and metastatic sites were similar in two treatment groups except a trend for more ECOG PS ≥ 2 patients in CP1 (34%). There was a male predominance in both groups. Contralateral lung metastases were higher in CP3 ($p = 0.040$). Three patients, with asymptomatic CNS metastases, were all treated in CP1. Median weekly paclitaxel dosage was 80 mg/m^2 and was similar in both groups ($p = 0.694$).

Efficacy

Efficacy was similar between CP3 and CP1 in objective RR, median OS and PFS times (Table 2 and Fig. 2). CP3 had a median OS of 14 months whereas CP1 had 9 months ($p = 0.084$). Median PFS were 7 months and 4 months, respectively ($p = 0.109$). One year OS rate was insignificantly higher in CP3 (50.8% vs 21.4%, HR: 1.643 [95% CI 0.91–2.96]). Although OS was similar in all performance status, there was a longer survival trend in favor of CP3 (14 months vs 9 months, $p = 0.053$) in patients with good performance status (ECOG PS < 2) (Table 3).

Toxicities

Table 4 summarizes the toxicities. There was an increased incidence of grade 3–4 anemia and grade 3–4 neutropenia in CP1 ($p = 0.003$ in both). There were no major differences in febrile neutropenia and infection toxicity profiles between two groups. Weekly schedule had tendency of increased grade 3–4 neurotoxicity (33.3% vs 42.9%, $p = 0.461$). Dose

Table 1 Demographical and clinical features of the groups

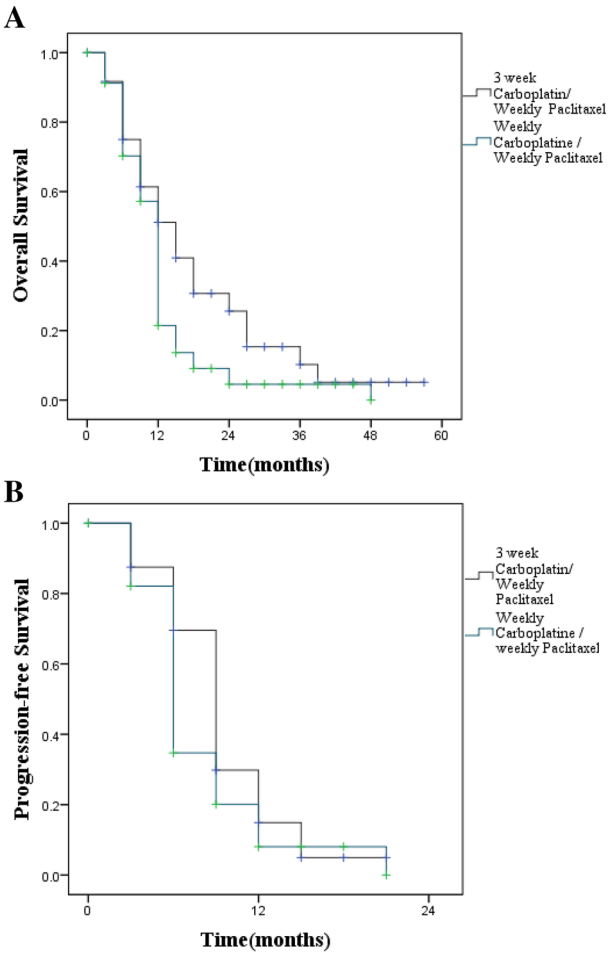
	CP3 3 weekly carboplatin/ weekly paclitaxel *n* = 24 (%)	CP1 Weekly carboplatin/ paclitaxel *n* = 35 (%)	*p*
Age, years, median (range)	71 (65–78)	73 (65–86)	0.172
Gender			0.385
Female	1 (4.2)	5 (14.3)	
Male	23 (95.8)	30 (85.7)	
Histopathologic subtypes			0.582
NOS	6 (25)	5 (14.3)	
Adenocarcinoma	7 (29.2)	12 (34.3)	
Squamous cell cancer	11 (45.8)	18 (51.4)	
ECOG PS			0.059
0–1	21 (87.5)	23 (65.7)	
≥ 2	3 (12.5)	12 (34.3)	
Weekly paclitaxel dosage, median (range)	80 (60–80)	80 (60–80)	0.694
Site of metastasis:			
Bone metastases	10 (41.7)	16 (45.7)	0.758
Liver metastases	9 (37.5)	7 (20)	0.137
Brain metastases	0	3 (8.6)	0.264
Contralateral lung metastases	14 (58.3)	11 (31.4)	***0.04***
Adrenal metastases	5 (20.8)	10 (28.6)	0.503
Malignant pleural effusion	6 (25)	7 (20)	0.649

Table 2 Efficacy of treatment groups

	CP3	CP1	*p*
Objective response rate (%)	20.9	29.4	0.465
Complete response rate (%)	4.2	2.9	0.803
Stable disease rate (%)	16.7	14.7	0.842
Partial response rate (%)	16.7	26.5	0.379
Progressive disease rate (%)	62.5	50	0.347
Median OS (months)	14	9	0.084
1 year OS (%)	50.8	21.4	95% CI 0.91–2.96
Median PFS (months)	7	4	0.109

Objective response rate = partial response + complete response

OS overall survival, *PFS* progression free survival, *PS* ECOG performance status



OS, overall survival; PFS, progression-free survival.

Fig. 2 **a** OS and **b** PFS of CP3 and CP1. *OS* overall survival, *PFS* progression-free survival

Table 3 Survivals according to ECOG PS

Variable	ECOG < 2		ECOG ≥ 2	
	CP3 (*n* = 21)	CP1 (*n* = 23)	CP3 (*n* = 3)	CP1 (*n* = 11)
OS (months)	14 (8.9–19.1)	9 (7.0–10.9)	8 (0.0–16.0)	9 (1.5–16.5)
p	0.053		0.073	
PFS (months)	7 (5.4–8.6)	5 (3.8–6.2)	7 (0.0–15.0)	3 (1.9–4.1)
p	0.249		0.448	

Table 4 Toxicity profiles of two platine based chemotherapy regimens

Hematologic toxicity, grade III/IV	CP3 *n* = 24 (%)	CP1 *n* = 35 (%)	*p*
Anemia	**10 (41.7)**	3 (8.6)	*0.003*
Neutropenia	**12 (50)**	5 (14.3)	*0.003*
Thrombocytopenia	1 (4.2)	1 (2.9)	0.999
Non-hematologic toxicities			
Febrile neutropenia	6 (25)	4 (11.4)	0.289
Venous thrombosis	2 (8.3)	4 (11.4)	0.999
Infection	7 (29.2)	9 (25.7)	0.770
> Grade 2 neurotoxicity	8 (33.3)	15 (42.9)	0.461
> Grade 2 diarrhea	3 (12.5)	7 (20)	0.506
> Grade 2 emesis	5 (20.8)	6 (17.1)	0.745
Dose delays/Skipped cycles	11 (45.8)	16 (45.7)	0.993
Dose reductions treatment	**11 (45.8)**	7 (20)	*0.034*
Discontinuation of chemotherapy	6 (25)	11 (32.4)	0.545

Italic values represent statistically significant side effects

Bold values represent side effects significantly seen more frequently

reduction of 10%–25% was more frequent in CP1 (45.8%) ($p = 0.034$). Treatment discontinuation and skipped cycles due to any reason were similar in both groups.

Discussion

Population is aging all around the world and median age for NSCLC is also increasing. Evidence based treatment is not well defined in elderly NSCLC patients with advanced disease due to higher prevalence of comorbidities, frailty, functional organ aging especially with worsening of kidney functions and declining of performance in daily activities [10]. Also some physicians are prejudice to treat senior patients and elderly patients are also under represented in randomized clinical studies. There are very few trials which addresses optimal first-line treatment choice in senior NSCLC patients [4, 12, 15] (Table 5). ELVIS study was the first randomized

Table 5 Chemotherapy trials in metastatic NSCLC studies in elderly patients including carboplatin and paclitaxel combination

Study	Schedule	*n*	OS	*p*	PFS	*p*	Neutropenia Grade 3/4 (%)	FEN Grade3/4 (%)	Neuropathy Grade3/4 (%)
ELVIS trial Gridelli [4] ≥ 70 years	BSC vs vinorelbine (30 mg/m^2) D1, 8/21D max. of 6 cycles	154	21 wk vs 28 wk	0.03	NA vs NA		10	NA	NA
Ricci et al. [19] 70 years	Gemcitabine (1000 mg/m^2) D1,8,15/28D for 6 cycles	46	6.75 mo	95% CI: 5.3–8.2	5.1 mo	95% CI 3.5–6.7	0.5	NA	NA
WJTOG9904 Kudoh et al. [20] ≥ 70 years	Docetaxel (60 mg/m^2) D1/21D vs vinorelbine (25 mg/m^2) D1,8/21D	182	14.3 mo vs 9.9	$p = 0.138$	5.5 mo vs 3.1	$p < 0.001$	82.9 vs 69.2	12.5 vs 11	0 vs 0
IFCT-0501; Quix et al. [7] ≥ 70 years	Carboplatin (AUC 6) D1 + paclitaxel (90 mg/m^2) D1,8,15 vs vinorelbine or gemcitabine	225 vs 226	10.3 vs 6.2 mo	< 0.0001	6.0 vs 2.8 mo	< 0.0001	48.4 vs 12.4	9.4 vs 2.7	3.1 vs 0.4
Ramalingam et al. [12] ≥ 70 years	Carboplatin (AUC 6) + paclitaxel 100 mg/m^2 D1,8,15/28D vs carboplatin (AUC 6) + paclitaxel 225 mg/m^2 D1/21D	136	37 wk vs 31 wk	NS	18.4 wk vs 12.7 wk	NS	17 vs 16	NA	5.5 vs 9.5
Ramalingam et al. [13] (subanalysis) ≥ 70 years stage IIB/IV	Carboplatin (AUC 6) D1 + paclitaxel 100 mg/m^2 D1,8,15/28D vs carboplatin (AUC 2) + paclitaxel 100 mg/m^2 D1,8,15/28D vs carboplatin (AUC 2) + paclitaxel 150–100 mg/m^2 wkly for 6 of 8 wk	390	11.3 mo vs 6 mo vs 14.4 mo	NS	7.2 mo vs 5.3 mo vs 8.6 mo	NS	13.6 vs 2.9 vs 12.1	2.3 vs 2.9 vs 3	6.9 vs 2.9 vs 12.2

Table 5 (continued)

Study	Schedule	*n*	OS	*p*	PFS	*p*	Neutropenia Grade 3/4 (%)	FEN Grade3/4 (%)	Neuropathy Grade3/4 (%)
Fidias et al. [21] ≥ 70 years stage III/IV	Carboplatin (AUC 2) + paclitaxel 90 mg/m^2 wkly for 6 of 8 wk	35	10.3 mo	NA	5.3mo	NA	5.8	NA	17.6
Volk et al. [22] ≥ 70 years	Weekly carboplatin (AUC 3) + paclitaxel (75 mg/m^2)	90	6.3 mo	0.58	4.1mo	0.36	14	NA	6
CALGB 9730 Lilenbaum et al. [5, 24]	Carboplatin (AUC 2.5) + paclitaxel (35 mg/m^2) D1,8/21D vs paclitaxel (225 mg/m^2) D1	155	8.0 mo vs 5.8 mo	0.289	NA	NA	NA	NA	NA
Kivrak et al. ≥ 65 years	Carboplatin (AUC 6) D1 + paclitaxel 75–100 mg/m^2 D1,8,15/21D vs carboplatin(AUC 2) + paclitaxel 75–100 mg/m^2 D1,8,15/21D	59	14 mo vs 9 mo	0.084	7 mo vs 4 mo	0.109	50 vs 14.3	25 vs 11.4	33.3 vs 42.9

FEN febrile neutropenia, *NA* not available, *NS* not significant, *mo* month, *wk* week

phase III single agent trial designed for elderly patients [4]. In this study 7 weeks of OS improvement was reported in vinorelbine group compared to best supportive care (BSC). Ricci et al. [17]. showed a 6.75 months of a median OS (95% CI 5.3–8.2) and 5.1 months of a median PFS (95% CI 3.5–6.7) with gemcitabine monotherapy in elderly patients. In WJTOG9904 study [18], no differences were observed between first line docetaxel or vinorelbine treatments on behalf of OS (14.3 months vs 9.9 months respectively, $p = 0.138$). But they showed PFS improvement with docetaxel (5.5 months vs 3.1 months respectively, $p < 0.001$) accompanied by increased neutropenia. After reports showing benefit of single agent treatments [4, 19, 20], platinum based combinations were also reported to be better [7, 19]. Carboplatin–paclitaxel combinations showed satisfactory efficacy with reasonable toxicity [7, 12, 13, 19]. In order to decrease toxicity and increase tolerability in senior patients, weekly schedules of paclitaxel have been developed [13, 17, 18, 21, 22]. Still, approximately one-third of elderly patients were referred to supportive care [23].

Our study is the first study in literature which compares the toxicity and efficacy of weekly paclitaxel with 3 weekly carboplatin versus weekly paclitaxel with weekly carboplatin schedule to our knowledge. Although our data is retrospective, objective response rates are similar with previous reports [12–14]. IFCT-0501 study reported 6 months of mPFS and 10.3 months of mOS with 3 weekly carboplatin (AUC of 6) and weekly paclitaxel (90 mg/m^2) which were shorter than our results (7 months and 14 months respectively) [7]. Schuette et al. compared weekly schedule (carboplatin AUC of 2 with paclitaxel 100 mg/m^2) and standard every-3-week schedule (carboplatin AUC of 6 with paclitaxel 200 mg/m^2) and found no survival differences (mPFS 6 months vs 7 months respectively; and mOS 9 months in both schedules) in all age population. Unlike our results, they reported higher neuropathy in 3 weekly schedule [15]. Ramalingam et al. also reported increased neuropathy with 3 weekly carboplatin and weekly paclitaxel regimen [12]. Grade III/IV neurotoxicity was 43% in weekly schedule and 33% in 3 weekly schedule in our study ($p = 0.461$). Grade III/IV neutropenia and anemia were also increased in 3 weekly schedule ($p = 0.003$ in both toxicities) in our study. In comparison with previous studies grade III/IV neutropenia and anemia in CP1 were more than expected in our study [6, 12, 14] (Table 5). These increased toxicities might be the cause of increased rate of dose reduction in CP1. In contrast with increased neutropenia in CP1, febrile neutropenia and infection rates are not increased. Elder patients with ≥ 2 ECOG PS have been usually excluded in previous studies [6, 11, 12, 14, 15]. Sweeney et al. [25]. studied the efficacy and toxicity of four different doublet chemotherapeutics in patients with advanced NSCLC according to performance status stratification. They reported better mOS with cisplatin–paclitaxel and cisplatin–gemcitabine treatments than carboplatin–paclitaxel combination (7.4 and 7.9 months vs 4.6 months respectively) and more adverse reactions than carboplatin–paclitaxel combination in PS 2 patients. They concluded that ECOG PS 2 patients experienced substantial number of adverse events and poor OS. In spite of our patient populations' ECOG PS being 0–3 which reflects routine daily practice, survivals seem longer with similar chemotherapy protocols in our patients.

Limitations of our study are as follows: Retrospective nature of our study and low numbers of patients are limitations resulting in possible selective bias and underreporting toxicity. Treatment groups were not well balanced which might impact negatively on results.

Conclusions

Elderly patients with metastatic NSCLC benefit from standard treatments as much as the others. Optimum first line treatment in seniors with advanced NSCLC has not been well defined. Comparison of standard 3 weekly and weekly regimens are limited. Our study is one of the first ones in the literature to our knowledge. Weekly carboplatin and paclitaxel might be more tolerable and is as effective as 3 weekly carboplatin and weekly paclitaxel schedule in metastatic elderly NSCLC patients.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

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