CARBOPLATIN-PACLITAXEL CHEMORADIOTHERAPY WITH 66 GY FOR ELDERLY PATIENTS WITH LOCALLY ADVANCED NON-SMALL-CELL LUNG CANCER

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Abstract

Background/Aim:

The common radiation dose administered with chemoradiotherapy for stage III non-small-cell lung cancer (NSCLC) is 60 Gy. We aimed to examine the feasibility and effectiveness of carboplatin-paclitaxel chemoradiotherapy with 66 Gy for elderly NSCLC patients.

Patients and Methods:

Forty-five patients with stage III NSCLC were enrolled from 2011 to 2014 at our hospital. They were divided into three groups according to their status and underwent different treatments. Overall survival (OS), progression-free survival (PFS), and local control (LC) were determined. Toxicity was evaluated with NCI-CTCAE ver. 4.0; intergroup differences were analysed statistically.

Results:

The group receiving carboplatin-paclitaxel chemotherapy with 66 Gy showed the longest median OS (40.4 months), PFS (17.9 months), and LC (44.3 months). Toxicity was acceptable in all groups.

Conclusion:

For elderly patients with stage III NSCLC, carboplatin-paclitaxel chemoradiotherapy with 66 Gy is suggested to be feasible and effective.

Key Words: Carboplatin-paclitaxel chemoradiotherapy, elderly patients, NSCLC, dose escalation

Introduction

Concurrent chemoradiotherapy (CCRT) has been the standard treatment for patients with unresectable stage III non-small-cell lung cancer (NSCLC) showing a good performance status (PS) [1,2]

Elderly patients and patients with a poor PS have high risks of adverse events after CCRT, so thoracic RT alone is also standard treatment for such patients. The 5-year survival rates for CCRT and RT alone were reported to be 25% and <10%, respectively [3].

The common chemotherapy regimens used concurrently with thoracic RT are platinum-based, doublet chemotherapies [4], and a total radiation dose of 60 Gy in 30 fractions is considered appropriate. Compared to cisplatin-based chemotherapy, the carboplatin-paclitaxel regimen has been reported to be equally efficacious and to exhibit a more favorable toxicity profile [5-9]. However, the rate of radiation pneumonitis associated with the latter has been reported to be higher than those associated with other regimens [10-12].

Dose escalation benefits are limited [13,14]. Based on the results of a phase III study (RTOG 0617), chemoradiotherapy with 74 Gy is not recommended [14]; however, the most suitable dose remains unknown.

In our hospital, we choose concurrent carboplatin-paclitaxel chemoradiotherapy with a total dose of 66 Gy in patients with high risks such as elderly patients or patients with a poor PS.

We aimed at verifying the validity of this therapy compared with cisplatin-based chemotherapy with 60Gy.

Materials and Methods

Patient population

This study was approved by the Institutional Ethics Committee of our institution and was performed in accordance with the Declaration of Helsinki.

All data were analyzed retrospectively. From January 2011 to January 2014, 144 consecutive NSCLC patients were treated with conventional RT using three-dimensional RT (3D-CRT) planning. Patients with resectable stage III NSCLC and who received palliative RT despite having stage III NSCLC were omitted. Thus, we analyzed 45 patients with unresectable stage III NSCLC who received curative CCRT or RT alone. NSCLC staging was per the Union for International Cancer Control TNM classification (7th edition). Patient characteristics are shown in Table 1.

Table 1. Patient characteristics (n = 45)

Characteristics		n
Age (years)	Median (range)	69 (42-79)
Sex	M	39
	F	6
Performance status	0/1/2/3/4	31/12/1/1/0
Histology	Adenocarcinoma	11
	Squamous cell carcinoma	20
	Large cell carcinoma	1
	Non-small-cell carcinoma	13
Stage	IIIA	27
	IIIB	18
Follow up	Median (All cases) (months)	32.8
Follow up	Median (Survivors) (months)	65.7

Treatment groups

The patients were divided into the following treatment groups according to age, Eastern Cooperative Oncology Group PS, and complications. Treatment outcomes and toxicity among the groups were evaluated.

Group CD: Patients who were younger than 70 years, with PS of 0 or 1, and without any major complications, and who received concurrent cisplatin-docetaxel chemotherapy (CD therapy)

and RT with a total dose of 60 Gy/30 fractions.

Group CP: Patients aged 70 years or higher, with PS 0 or 1, and without any major complications, or younger than 70 years but with PS 2 or higher, or with complications, and who received concurrent carboplatin-paclitaxel chemoradiotherapy with a total dose of 66 Gy/33 fractions.

Group RT: Patients aged 70 years or higher, with PS 2 or higher, or with complications, and who received RT alone with a total dose of 70 Gy/35 fractions (Table 2).

Table 2. Details of the three chemoradiotherapy groups

	Patients (n)	Radiotherapy	Chemotherapy	Age	PS	Complications
Group CD	11	60 Gy/30 fr	CDDP+DTX	<70	PS 0 or 1	None
Group CP	24	66 Gy/33 fr	CBDCA+PTX	>=70	PS 0 or 1	None
				<70	PS 2 or higher	Found
Group RT	10	70 Gy/35 fr	None	>= 70	PS 2 or higher	Found

CDDP+DTX: Cisplatin-Docetaxel
CBDCA+PTX: Carboplatin-Paclitaxel
PS: ECOG performance status

Radiation therapy

We performed conventional RT using 3D-CRT planning, and elective mediastinal nodal irradiation was within the acceptable range of the total lung dose. Furthermore, we used the anterior-posterior opposing technique (Group CD: 40 Gy, CP: 42 Gy, RT: 44 Gy) and then the oblique opposing technique to cut the spinal cord. V20 (the percentage of lung volume receiving a dose higher than 20 Gy) was generally determined as follows: Groups CD and CP, V20 $\leq$ 30%; Group RT, V20 $\leq$ 35%.

Toxicity

We evaluated the toxicity in the groups with NCI Common Terminology Criteria for Adverse Events ver. 4.0.

Statistical analysis.

We measured the survival duration and the no-exacerbation days from the final RT day and estimated the overall survival (OS), progression-free survival (PFS), and local control (LC). In our analyses, dropout cases were regarded as mortality. Differences in these indices were statistically analyzed with EZR (ver. 1.32; Saitama Medical Center, Jichi Medical University, Saitama, Japan) which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [15]. The Kaplan–Meier method was used to calculate the OS and PFS; the Gray-Fine method was used to determine the LC. The log-rank test was used to calculate significant differences. A P-value of less than 0.05 was considered as significant for each of the statistical analyses.

Results

Survival and response.

The median follow-up periods for all and surviving patients were 32.8 and 65.7 months,

respectively. The median OS in the CD, CP, and RT groups was 37.3, 40.4, and 20.9 months, respectively (Fig.1). The corresponding 3-year OS rates were 54.5% (95% CI, 22.9–78.0), 54.2% (95% CI, 32.7–71.4), and 10% (95% CI, 0.6–35.8) (P > 0.05). The 5-year OS rate for the chemotherapy groups (CD and CP) was 35.7% (95% CI, 20.0–51.7) and that for the group without chemotherapy (RT) was 10% (95% CI, 0.6–35.8) (P = 0.03). The median PFS rates in the CD, CP, and RT groups were 8.8, 17.9, and 8.9 months, respectively (Fig.2). The corresponding 3-year PFS

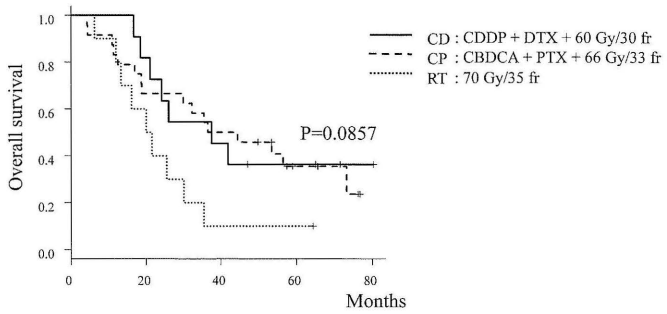

Fig. 1. Overall survival. The CD and CP groups had better overall survival (OS) than did the RT group.
CDDP+DTX: Cisplatin-Docetaxel
CBDCA+PTX: Carboplatin-Paclitaxel

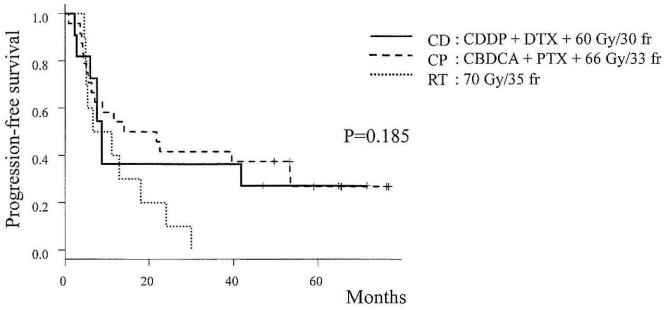

Fig. 2. Progression-free survival. The CD and CP groups had better progression-free survival (PFS) than did the RT group.
CDDP+DTX: Cisplatin-Docetaxel
CBDCA+PTX: Carboplatin-Paclitaxel

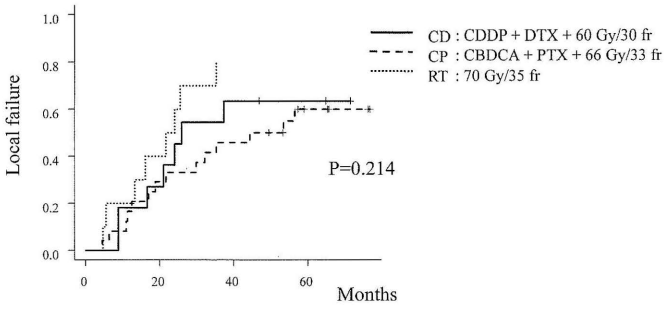

Fig. 3. Local failure. Local failure was the worst in the RT group. CCRT was associated with long-term tumor control.
CDDP+DTX: Cisplatin-Docetaxel
CBDCA+PTX: Carboplatin-Paclitaxel

rates were 36.4% (95% CI, 11.2–62.7), 41.7% (95% CI, 22.2–60.1), and unknown. We evaluated LC in terms of the time until local failure (LF). The median time until LF was 25.9, 44.3, and 22.8 months, respectively, in the CD, CP, and RT groups (Fig.3). The corresponding 3-year LF rates were 54.5% (95% CI, 20.6–79.2), 45.8% (95% CI, 25.0–64.5), and unknown. Intergroup differences in indices were not significant ($P > 0.05$); however, the CP group showed a tendency of better results for all indices. Table 3 shows the recurrence sites and rates in each group. The non-recurrence rates in the CD, CP, and RT groups were 36.3%, 37.5%, and 10.0%, respectively.

Table 3. Recurrence sites and numbers in each group

Recurrence site	Group CD		Group CP		Group RT	
	n	%	n	%	n	%
Local failure	2	18.2	3	12.5	4	40
Thoracic Lymph node	2	18.2	3	12.5	0	0
Brain	1	9.1	1	4.2	0	0
Bone	0	0	2	8.3	0	0
Adrenal gland	1	9.1	2	8.3	0	0
Lung	0	0	3	12.5	3	30
Liver	0	0	1	4.2	0	0
Muscle	1	9.1	0	0	0	0
Pleural dissemination	0	0	0	0	2	20
No recurrence	4	36.3	9	37.5	1	10
Total	11	100	24	100	10	100

Toxicities

Grade 5 toxicity was not noted. Pneumonitis was slightly severe in the CP group. The rate of grade 3 or 4 severe pneumonitis and esophagitis was 4.4%, each, in all patients. Myelosuppression was more severe in the CD and CP groups; the rate of grade 3 or 4 myelosuppression was 25.7% in both groups (Table 4).

Table 4. Toxicities were acceptable in all groups. Myelosuppression was noted in the CP and CD groups. There was no grade 5 toxicity. (n=45)

	Grade <= 2 (n)			Grade 3 (n)			Grade 4 (n)		
	CD	CP	RT	CD	CP	RT	CD	CP	RT
Pneumonitis	11	22	10	0	2	0	0	0	0
Esophagitis	10	23	10	1	1	0	0	0	0
Myelosuppression	9	17	10	2	5	0	0	2	0

Discussion

Concurrent carboplatin-paclitaxel chemoradiotherapy with a total dose of 66 Gy was not inferior in terms of therapeutic effect and toxicity compared with cisplatin-based chemotherapy with 60 Gy.

In the previous study, the 3- and 5-year Kaplan–Meier OS rates with concurrent carboplatin-paclitaxel chemoradiotherapy with a total dose of 66 Gy were 52.2% (95% CI 37.0 to 65.4) and 34.0% (95% CI 20.1 to 48.5) [16], respectively. The findings suggested that combined therapy

was feasible and efficacious for stage III NSCLC. In this retrospective study, we compared the outcomes and toxicity of groups CD, CP, and RT comprising patients with unresectable stage III NSCLC. Compared to the CD group, the CP group had elderly patients and those with poorer PS; nevertheless, the latter achieved similar or slightly better survival outcomes. Toxicity resulted in a slightly higher but tolerable risk of radiation pneumonitis in the CP group.

There is no clear evidence to define the optimal radiation dose and fractions for thoracic RT alone for stage III NSCLC patients with poor PS. We prescribed 70 Gy with V20 values of ≤ 35% based on previous dose-escalation trials [13,17,18]. The results of the RT group were almost the same as those reported previously [1,6]. According to a phase 3 trial by the Japan Clinical Oncology Group (JCOG0301) [19], for patients older than 70 years with locally advanced NSCLC, combination chemoradiotherapy provides significantly better OS than that associated with RT alone. The efficacy of CCRT in elderly patients has been confirmed [20].

Overall, OS, PFS, and LC in the CD and CP groups were better than those in the RT group; toxicity was tolerable, and grade 5 toxicity was not noted. Radiation pneumonitis was less severe than that in studies that showed that elderly patients who underwent carboplatin-paclitaxel chemotherapy were at high risk of radiation pneumonitis. The risk of radiation esophagitis, however, was the same [10-12,21]. The findings seem attributable to the fact that 3D-CRT was used in this study to increase the tumor dose while minimizing toxic effects on normal tissue and that the patients' PS was mostly good, i.e. 0 or 1.

There was no significant difference between the CD and CP groups; however, the CP group tended to show better treatment benefits and tolerable toxicity. Compared to the CD group, the CP group had older patients or those with slightly poorer PS; however, the therapeutic effect was equally efficacious, and toxicity was acceptable. Carboplatin-paclitaxel is considered an acceptable CCRT regimen, even in older patients or patients with comorbidities [9,12].

This study has several limitations such as the small number of patients and its retrospective nature; furthermore, there might be some selection bias.

In conclusion, concurrent carboplatin-paclitaxel chemoradiotherapy with a total dose of 66 Gy/33 fractions has potential for application in the management of unresectable stage III NSCLC among elderly patients or those with poor PS. Further studies are needed on the association between radiation doses, fractionation, and fields, and chemotherapy regimens for patients with unresectable stage III NSCLC, especially elderly patients or those with poor PS.

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Conflict of Interest

The authors do not have any conflicts of interest associated with this study.

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