Weekly administration of paclitaxel and carboplatin with concurrent thoracic radiation in previously untreated elderly patients with locally advanced non-small-cell lung cancer: A case series of 20 patients

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Abstract. Elderly patients with stage III non-small-cell lung cancer (NSCLC) are frequently underrepresented in clinical trials that evaluate chemoradiotherapy, due to their poor functional status, coexisting illnesses and limited life expectancy. The Japan Clinical Oncology Group 0301 trial (JCOG0301) was the first study to demonstrate that thoracic radiation therapy (TRT) with daily low-dose carboplatin may improve the outcome of elderly patients with stage III NSCLC. However, the efficacy and safety profiles of chemoradiotherapy, including platinum doublets, have not been clearly determined in this patient population. We retrospectively assessed the efficacy and toxicity of weekly paclitaxel in combination with carboplatin and concurrent TRT in patients aged ≥75 years with previously untreated locally advanced NSCLC. Between February, 2004 and July, 2013, we collected the data of 20 patients treated with weekly paclitaxel and carboplatin for 6 weeks and concurrent TRT. The objective response rate was 90%, the disease control rate was 95%, the median progression-free survival was 8.63 months [95% confidence interval (CI): 5.7-16.7] and the median overall survival (OS) was 16.1 months (95% CI: 10.7-41.6). There were no grade 4 hematological or non-hematological toxicities and no reported treatment-related deaths. Therefore, platinum doublet therapy in combination with TRT did not provide a clinically significant survival benefit in our population of elderly patients with locally advanced NSCLC. However, the present study demonstrated the good feasibility and safety of this regimen. Further prospective clinical trials are required to evaluate the efficacy and safety of platinum doublet with TRT in elderly patients.

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Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide (1). This disease is more common among the elderly, with >2/3 of lung cancer cases occurring in individuals aged ≥65 years and a median age at diagnosis of 70 years (2). The majority of lung cancer patients present with unresectable disease and are candidates for thoracic radiation therapy (TRT) and/or chemotherapy. Previously randomized clinical trials revealed a survival benefit for concurrent vs. sequential chemoradiotherapy (3,4) and for sequential chemoradiotherapy vs. radiotherapy alone for patients with stage III non-small-cell lung cancer (NSCLC) (5,6).

Concurrent chemoradiotherapy with platinum-based doublet chemotherapy is currently considered as the standard treatment for patients with inoperable stage III NSCLC. However, data from the Surveillance Epidemiology and End Results database reveal that the majority of elderly patients do not receive combined modality treatment (7). This finding may reflect the uncertainty regarding concurrent chemoradiotherapy as a treatment for elderly patients with locally advanced NSCLC.

In elderly patients, the use of concurrent chemoradiotherapy is often limited by poor functional status, coexisting illnesses, limited life expectancy and the physicians' concerns regarding toxicity and the effect of the treatment on the quality of life (QOL) of the patients. In addition, the number of available

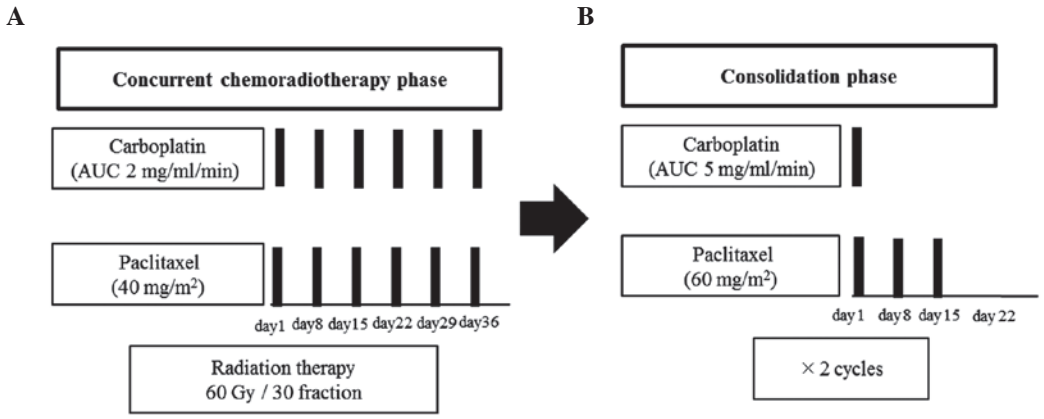

Figure 1. Chemotherapy schedule. (A) Concurrent chemoradiotherapy phase: paclitaxel (40 mg/m^2) and carboplatin area under the curve (AUC) at 2 mg/ml/min were administered concomitantly on the first day of the week. (B) Consolidation phase: weekly paclitaxel (70 mg/m^2) for 3 of 4 weeks with carboplatin (AUC, 5 mg/ml/min) on day 1 of each 4-week cycle.

clinical trials designed to specifically evaluate the treatment of elderly patients with stage III NSCLC is limited. Therefore, it is crucial to establish an effective and feasible chemoradiotherapy regimen for elderly patients with stage III NSCLC.

The Japan Clinical Oncology Group 0301 trial (JCOG0301) recently reported a significant survival advantage for elderly patients who received chemoradiotherapy (daily low-dose carboplatin plus radiotherapy) for locally advanced NSCLC (8). That trial provided reasonably strong evidence that single-agent carboplatin-based chemoradiotherapy is well-tolerated by elderly patients with locally advanced NSCLC and may achieve improved survival rates compared to radiotherapy alone. However, it has not been determined whether a carboplatin-based doublet regimen with TRT is feasible for elderly patients with locally advanced NSCLC.

The present study focused on the effectiveness of weekly paclitaxel in combination with carboplatin and concurrent TRT, since the efficacy and safety of this regimen in younger patients with locally advanced NSCLC was confirmed by phase III trials (9). The aim of our retrospective analysis was to assess the anticancer effect and toxicity of weekly paclitaxel and carboplatin with concurrent TRT in patients aged ≥75 years with previously untreated locally advanced NSCLC.

Patients and methods

Patients. This retrospective study was performed at the Institute of Biomedical Research and Innovation and the Kobe City Medical Center General Hospital, Hyogo, Japan. The data from 20 consecutive patients, aged ≥75 years, who were treated with weekly paclitaxel and carboplatin for 6 weeks, plus TRT (60 Gy) for locally advanced unresectable NSCLC (stage IIIA or IIIB) between February, 2004 and July, 2013 were retrospectively evaluated. This study was approved by the Institutional Review Board of the two hospitals.

The diagnosis of locally advanced unresectable stage III NSCLC was confirmed by a multidisciplinary council consisting of radiologists, radiation oncologists and medical oncologists prior to the initiation of the treatment. All the patients were diagnosed with NSCLC and the diagnosis was histopathologically confirmed. Tumour staging was performed by chest radiography, computed tomography (CT) scan or magnetic resonance imaging of the head, CT scan of the chest and the abdomen, CT scan or ultrasonography of the abdomen and bone scintigraphy or fluorodeoxyglucose positron emission tomography and CT scan. The patients were staged according to the tumour-node-metastasis (TNM) classification (10). An Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2 was required for inclusion in this study (11).

Radiotherapy. Radiotherapy for all the patients consisted of 60 Gy administered as 30 fractions over 6 weeks. A total of 40 Gy was delivered with 6-10 MV photons using anterior-posterior opposed fields that included the primary tumour, metastatic lymph nodes and regional nodes. A booster dose of 20 Gy was delivered to the primary tumour and the metastatic lymph nodes with off-cord fields, for a total dose of 60 Gy. Three-dimensional CT simulation was used for treatment planning. The clinical target volume included the gross tumour volume, including the primary tumour and metastatic nodes (>1 cm at the shortest dimension), plus a 0.5-cm margin. The regional nodes, excluding the contralateral hilar nodes, were also included in the clinical target volume. The planning target volumes for the primary tumour, metastatic lymph nodes and regional nodes were calculated as the clinical target volume plus adequate margins (typically 0.5-1.0 cm laterally and 1.0-2.0 cm craniocaudally).

The treatment plan was designed not to exceed the maximum doses tolerated by intrathoracic structures, such as the lung, spinal cord and heart. The spinal cord was excluded from the boost field by the oblique opposing method. If the dose of the spinal cord exceeded 40 Gy when planning the treatment, the minimum dose of the planning target volumes was modified and the dose to the spinal cord was restricted within 40 Gy. Patients were excluded from this study if the initial radiation field exceeded half of the ipsilateral lung. If ≥grade 3 oesophagitis occurred and the physician decided that the RT could not be continued, the treatment was suspended and reinitiated following recovery of the oesophagitis to ≤grade 2.

Chemotherapy. The treatment schedule is shown in Fig. 1. During radiotherapy, paclitaxel (40 mg/m^2) and carboplatin

area under the curve (AUC) at 2 mg/ml/min were administered concomitantly on the first day of the week. The consolidation phase chemotherapy, initiated 3-4 weeks after the concurrent chemoradiotherapy, was administered in 2 cycles. The consolidation chemotherapy consisted of 3 weekly cycles of paclitaxel (200 mg/m^2 administered over 3 h) followed by carboplatin (AUC, 5 mg/ml/min on day 1) or paclitaxel (70 mg/m^2) weekly for 3 of 4 weeks with carboplatin (AUC, 5 mg/ml/min) on day 1 of each 4-week cycle. During radiation treatment, paclitaxel and carboplatin administration was suspended if grade 4 hematological toxicity occurred and chemotherapy was reinitiated following recovery to ≤grade 3. A maximum of one dose level reduction was permitted per patient in the consolidation phase. The dose of carboplatin was reduced to achieve an AUC of 4 mg/ml/min and the dose of paclitaxel was reduced to 175 mg/m^2, or the weekly paclitaxel dose was reduced to 60 mg/m^2. Both paclitaxel and carboplatin were reduced by one dose level if grade 4 hematological or ≥grade 3 non-hematological toxicity occurred and the physician decided that chemotherapy should be discontinued.

Treatment and toxicity evaluation. The treatment efficacy and toxicity were assessed in all the treated patients. The patients were assessed for response by CT scans within 8 weeks of completing treatment. Following treatment completion, chest radiographs were obtained monthly and thoracic CT scans every 6 months. The patients underwent follow-up monthly for 1 year and at least every 3 months thereafter.

The treatment response evaluation was performed according to the Response Evaluation Criteria in Solid Tumours, version 1.09 (12), based only on the longest diameter of all the lesions as follows: Complete response (CR), disappearance of all the lesions; partial response (PR), ≥30% reduction of the sum of the longest diameters of all the lesions, referring to the sum of baseline longest diameters; progressive disease (PD), ≥20% increase in the sum of the longest diameters of the target lesions, referring to the smallest sum of the longest diameters recorded since the initiation of the treatment or the appearance of one or more new lesions; stable disease (SD), neither sufficient lesion shrinkage to qualify for PR, nor sufficient lesion growth to qualify for PD, referring to the smallest sum of the longest diameters since the initiation of the treatment. The toxicity was evaluated in accordance with the National Cancer Institute Common Toxicity Criteria 4.0.3 (13).

Statistical analysis. Median overall survival (OS) was defined as the time from the initiation of the treatment to death from any cause or the last follow-up. The patients who remained alive were evaluated at the date of the last follow-up. Progression-free survival (PFS) was defined as the time from the initiation of the treatment to disease progression (local recurrence and/or distant metastasis) or death. The respective contribution of local and distant progression to PFS and the rate of implementation of chemotherapy were estimated. The median follow-up time was calculated with the reverse Kaplan-Meier method and the Kaplan-Meier method was used for survival analysis. JMP software, version 9.0.0 (SAS Institute, Cary, NC, USA), was used for statistical analysis.

Table I. Patient characteristics (n=20).

Characteristics	Patients (%)
Median age, years (range)	78 (75-86)
Gender	
Male	17 (85)
Female	3 (15)
Histology	
Adenocarcinoma	8 (40)
Squamous cell carcinoma	12 (60)
ECOG performance status	
0	2 (10)
1	15 (75)
2	3 (15)
Disease stage	
IIIA	9 (45)
IIIB	11 (55)
Tumour stage	
1	2 (10)
2	7 (35)
3	4 (20)
4	7 (35)
Nodal stage	
1	2 (10)
2	12 (60)
3	6 (30)
Comorbidity	
Hypertension	5 (25)
Diabetes	2 (10)
Cerebrovascular disease	2 (10)
Arrhythmia	1 (5)
Ischemic heart disease	2 (10)
Smoking history	
Negative	2 (10)
Positive	18 (90)

ECOG, Eastern Cooperative Oncology Group.

Results

Patient characteristics. Between February, 2004 and July, 2013, the data of 20 patients who were treated with weekly paclitaxel and carboplatin for 6 weeks plus 60 Gy TRT, were collected at the two abovementioned institutions. The median follow-up for censored cases was 21.1 months (interquartile range, 16.0-21.6). The pretreatment characteristics of the patients are summarized in Table I. The median age of the patients was 78 years, 85% of the patients were men, 90% had a history of smoking and 85% had an ECOG PS of 0-1. A total of 45% of the patients had stage IIIA and the remaining 55% had stage IIIB disease. The reported comorbidities, listed by decreasing frequency, were hypertension (25%), diabetes (10%), cerebrovascular disease (10%), ischemic heart disease (10%) and arrhythmia (5%).

Table II. Chemotherapy administered.

Chemotherapy	Cycles	Patients (%)
Concurrent	3	1 (5)
	4	1 (5)
	5	6 (30)
	6	12 (60)
Consolidation	0	6 (30)
	1	2 (10)
	2	12 (60)

Table III. Objective response.

Type of response	Patients (%)
Complete	1 (5)
Partial	17 (85)
Stable disease	1 (5)
Progressive disease	1 (5)
Objective response rate	18 (90)
Disease control rate	19 (95)

Table IV. Adverse events reported during the entire course of the treatment.

	Toxicity (%)		
Adverse event	Grade 2	Grade 3	Grade 4
Leukopenia	8	8	0
Neutropenia	7	4	0
Anaemia	1	0	0
Thrombocytopenia	0	0	0
Pneumonitis	3	0	0
Esophagitis	5	0	0
Pleural effusion (non-malignant)	0	0	0
Sensory neuropathy	0	0	0
Vomiting	0	0	0
Diarrhea	0	0	0
Rash	1	0	0

Treatment. The compliance to the protocol was considered as acceptable. The status of chemotherapy implementation is shown in Table II . During the concurrent phase, 60% of the patients received 6 weekly cycles of chemotherapy. In the consolidation phase, 60% of the patients received the two scheduled courses of therapy. All the patients completed TRT with a total dose of 60 Gy.

Efficacy. In total, 1 patient achieved a CR, 17 achieved a PR, 1 had SD and 1 had PD (Table III). The objective response rate (ORR) was 90% and the disease control rate (DCR) was 95%. The PFS and OS of the patients who were included in the trial are shown in Fig. 2. The median PFS was 8.6 months [95% confidence interval (CI): 5.7-16.7] and the median OS was 16.1 months (95% CI: 10.7-41.6).

Toxicity. The treatment-related adverse events are shown in Table IV. There were no reported grade 4 hematological and non-hematological toxicities. Grade 3 leukopenia occurred in 8 (40%) and grade 3 neutropenia in 4 patients (20%). Grade 2 pneumonitis occurred in 3 patients (15%) on day 17 and at 3 and 7 months following treatment. All the cases required steroid therapy (prednisolone 20-40 mg/day). Grade 2 oesophagitis occurred in 5 patients (25%). There were no reported treatment-related deaths.

First site of disease progression. A total of 3 patients (15%) exhibited local relapse, 9 (45%) had distant metastasis and 2 (10%) had both. Overall, 16 patients (80%) exhibited disease progression and 17 (85%) succumbed to the disease during the analysis, with 14 deaths due to the primary disease and 1 due to acute myocardial infarction at 379 days after treatment.

Post-treatment. A total of 8 patients (40%) received second-line therapy (pemetrexed, 2; docetaxel, 1; gemcitabine, 1; vinorelbine, 1; S1, 1; gefitinib, 1; and erlotinib, 1). All the patients received palliative care and palliative radiation therapy as required.

Discussion

The present study retrospectively assessed the anticancer effect and toxicity of weekly paclitaxel in combination with carboplatin and concurrent TRT in previously untreated elderly patients (aged ≥75 years) with locally advanced NSCLC. According to our results, the ORR was 90% and the DCR was 95%, which were improved compared to those reported by previous studies. Furthermore, the median PFS was 8.6 months and the median OS was 16.1 months.

The PFS was similar to that reported by previous studies (8,9). The OS was different, although it was similar to that reported for radiation alone (16.9 months) in the JCOG0301 trial (8).

Concurrent chemoradiotherapy is considered to be the standard treatment for locally advanced NSCLC in selected patients with a good PS (14). Despite the high frequency of NSCLC in the elderly population, elderly patients are frequently underrepresented in clinical trials evaluating chemoradiotherapy (15,16). This is due to elderly patients generally being incapable of tolerating the treatment-related toxicity. In addition, the expectations for long-term benefits may be limited on the part of physicians, as well as on the part of the patients or their families. Therefore, the number of clinical trials designed to specifically study the treatment of elderly patients with stage III NSCLC is limited (17,18).

The results of age-based retrospective subgroup analyses of randomized phase III trials that evaluated concurrent chemoradiotherapy were previously reported by 5 studies (18-22). Those studies reported that healthy older adults with locally advanced NSCLC benefitted from concurrent chemoradiotherapy similar to younger patients, but experienced higher rates of hospitalization and toxicity. A previous meta-analysis

Table V. Results of previous studies and the present study.

Studies	Patient age, years median (range)	ORR (%)	PFS (months)	OS (months)	Grade 3 or worse AEs (%) (neutropenia/pneumonitis/esophagitis)	Refs.
WJTOG0105 weekly CBDCA+PAC arm	63 (38-74)	63.3	9.5	22.0	61.6/4.1/8.2	(9)
JCOG0301 chemoradiotherapy arm	77 (71-89)	51.5	8.9	22.4	57.2/1.0/1.0	(8)
Present study	78 (75-86)	90.0	8.6	16.1	20/0/0	-

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; AEs, adverse events; WJTOG, West Japan Thoracic Oncology Group; CBDCA, carboplatin; PAC, paclitaxel; JCOG, Japan Clinical Oncology Group.

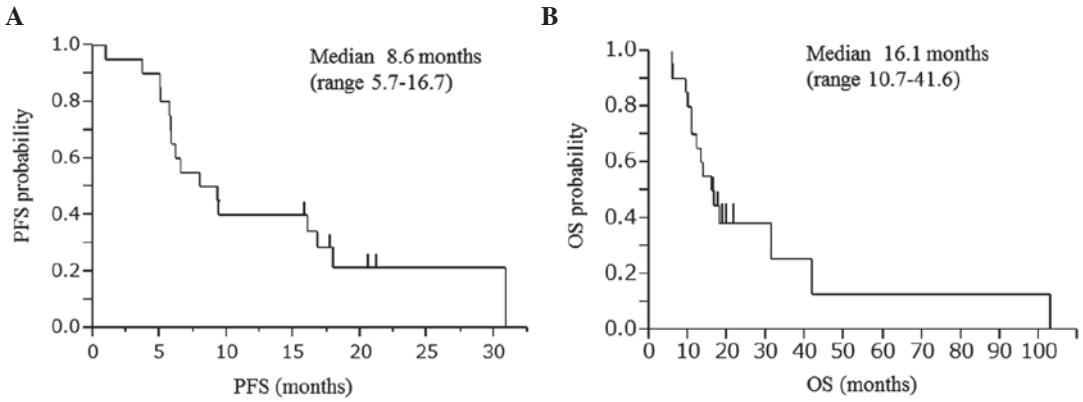

Figure 2. Kaplan-Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS).

reported that the benefit of concomitant chemotherapy appeared to be greater in elderly compared to that in younger patients (23).

In the JCOG0301 study, Atagi *et al* (8), reported that the median OS for the chemoradiotherapy (TRT with daily low-dose carboplatin) and radiation therapy alone groups were 22.4 and 16.9 months, respectively. Chemoradiotherapy was associated with a significantly longer survival compared to radiation therapy alone. That study was the first to demonstrate that combined chemoradiotherapy may improve the outcome of stage III NSCLC in elderly patients. In the present study, weekly paclitaxel and carboplatin with concurrent TRT did not provide a survival benefit when compared to the results of the JCOG0310 study.

The West Japan Thoracic Oncology Group (WJTOG0105), in a phase III trial, evaluated concurrent chemoradiotherapy using second-generation regimens at full doses or third-generation regimens at reduced doses in patients with locally advanced NSCLC aged <75 years. The results of that trial demonstrated that treatment with weekly paclitaxel and carboplatin with TRT was equally efficacious and exhibited a more favorable toxicity profile compared to the second-generation regimens (9). The ORR was 63.3%, the median PFS was 9.5 months and the median survival time and 5-year survival rate were 22.0 months and 19.8%, respectively, with the weekly paclitaxel and carboplatin treatment. In the WJTOG0105 study, the status of chemotherapy implementation was reported as 58.5% of patients who received 6 weekly cycles of chemotherapy during the concurrent phase and 49.7% of patients who received the two scheduled courses of therapy during the consolidation phase. The incidence of grade 3 or worse hematological toxicity was leukopenia in 66%, neutropenia in 61% and febrile neutropenia in 10.2% of the patients. Grade 3 or worse pneumonitis occurred in 4.1% and esophagitis in 8.2% of the patients in the weekly paclitaxel and carboplatin group.

The present study revealed a lower incidence of grade 3 or worse hematological toxicity, pneumonitis and esophagitis compared to those reported by the WJTOG0105 study for the weekly paclitaxel and carboplatin group. Although our study exhibited similar chemotherapy implementation, ORR, PFS and milder toxicity, it failed to demonstrate a survival benefit compared to other studies (Table V), indicating that our retrospective and small cohort group was not sufficient to provide statistically valid results. Concurrent TRT and chemotherapy with weekly paclitaxel and carboplatin is potentially an effective and feasible treatment for elderly patients; however, our retrospective cohort was insufficient to demonstrate efficacy. Future larger and well-designed prospective clinical trials are required to verify survival benefits.

The limitations of our study lie with its retrospective nature, the small cohort and the lack of a QOL assessment. The intervals between the evaluations of the lesions in this study were not as accurate as those in a prospective study. In addition, the severity of the adverse events may have been underestimated in the present study due to its retrospective nature. The patients

were hospitalized during most of the treatment period and the toxicity data were recorded in detail in the patients' medical records. The sample size in the present study was limited; therefore, it was difficult to reach a definitive conclusion. However, the collection of data on a large number of patients with locally advanced NSCLC, aged ≥75 years, treated with chemoradiotherapy, is difficult. This retrospective study may therefore be useful for physicians to determine the optimal treatment strategy for patients aged ≥75 years with locally advanced NSCLC.

Previous studies demonstrated that QOL is an important prognostic factor in patients with lung cancer (24-31). One randomized phase III study reported QOL as a prognostic factor for long-term survival among patients with locally advanced NSCLC treated with chemoradiotherapy (32). However, in elderly NSCLC patients, the adverse effects of chemoradiotherapy and their negative effect on the QOL have not been determined. QOL assessment is required for future clinical trials of chemoradiotherapy in elderly patients.

In conclusion, weekly paclitaxel and carboplatin with concurrent TRT failed to demonstrate a clinically significant survival benefit in elderly patients with locally advanced NSCLC. However, this regimen had a tolerable safety profile and an improved objective response. Therefore, it is suggested that this regimen may be suitable for elderly patients; however, further prospective clinical trials are required to evaluate the true efficacy and safety of weekly paclitaxel and carboplatin with concurrent TRT for the treatment of elderly patients with NSCLC.

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