International Journal of Clinical Oncology (2019) 24:1543–1548
https://doi.org/10.1007/s10147-019-01516-9

ORIGINAL ARTICLE

Weekly paclitaxel in combination with carboplatin for advanced non-small-cell lung cancer complicated by idiopathic interstitial pneumonias: a single-arm phase II study

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Received: 12 October 2018 / Accepted: 20 July 2019 / Published online: 27 July 2019
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Abstract

Background Idiopathic interstitial pneumonias (IIPs) are associated with increased risk of lung cancer. In Japan, acute exaberation of IIPs induced by anticancer treatment is a critical issue. For this reason, there is limited available evidence regarding the optimal treatment approach for lung cancer patients complicated with IIPs. Our previous prospective pilot study demonstrated the safety and efficacy of weekly paclitaxel in combination with carboplatin for advanced non-small-cell lung cancer (NSCLC) with IIPs. The current study was conducted to confirm the results of the same combination therapy used in a larger patient population.

Methods Chemotherapy-naïve patients with advanced stage or post-operative recurrent NSCLC patients complicated by IIPs were enrolled. Patients received paclitaxel (100 mg/m^2) on days 1, 8, and 15, and carboplatin (AUC 5.0) once every 4 weeks.

Results Thirty-three of 35 enrolled patients were evaluable for analysis and received a median of four treatment cycles (range 1–6). Four patients (12.1%; 95% confidence interval 3.4–28.2%) had acute exacerbation (AEx)-related IIPs to the study treatment. However, no fatalities due to AEx were observed. The overall response was 69.7%. The median progression-free survival, median survival time, and 1-year survival were 6.3 months, 19.8 months, and 55.4%, respectively.

Conclusions The efficacy of carboplatin plus weekly paclitaxel treatment for advanced NSCLC patients with IIPs was comparable to that of conventional chemotherapy in advanced NSCLC patients without IIPs. Moreover, the primary endpoint was set to the frequency of treatment-related acute exacerbation, and the primary endpoint was met. These results suggest that patients with advanced NSCLC complicated by IIPs may benefit from this combination chemotherapy.

Keywords Idiopathic pulmonary fibrosis · Acute exacerbation · Chemotherapy · Paclitaxel · Re-challenge

Introduction

Idiopathic interstitial pneumonias (IIPs) are associated with an independent increased risk of lung carcinogenesis [1]. In particular, the incidence of lung cancer in patients with idiopathic pulmonary fibrosis (IPF) is higher than that in the general population, whose relative risk is reportedly 7–14 [1–5]. Kawasaki et al. reported that IPF was pathologically identified in 7.5% of patients with surgically resected lung cancer [6].

Acute exacerbation (AEx) of IIPs, caused by anticancer treatment, is the most common lethal complication in Japanese patients with lung cancer. The frequency of acute deterioration of pre-existing interstitial lung disease (ILD), in patients receiving chemotherapy, has been reported to range from 20 to 28% [7–9]. For this reason, lung cancers with IIPs are regarded as high risk and poor prognosis, and excluded from clinical trials. Therefore, determining the regimen carrying the lowest risk of AEx is difficult and the treatment of these patients remains a challenge.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10147-019-01516-9) contains supplementary material, which is available to authorized users.

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We previously performed a prospective pilot study evaluating the safety and efficacy of weekly paclitaxel in combination with carboplatin using 18 advanced non-small-cell lung cancer (NSCLC) complicated by IIPs [10]. At the time of the pilot study, paclitaxel combined with carboplatin administered every 3 weeks was widely used for advanced NSCLC as the established standard regimen. To reduce the toxicity and complications, especially severe neutropenia causing infectious disease, we selected chemotherapy regimen based on weekly schedules with easily dose modification of paclitaxel. This study showed that response [objective response (ORR): 61%, median overall survival (OS): 10.6 months, and 1-year survival: 22%] was similar to that of standard chemotherapy for NSCLC without IIPs. In addition, the incidence of AEx of IIPs (5.6%) was lower than that reported in previous studies.

In this study, we performed the prospective, single-arm, phase II study to confirm the clinical safety and efficacy of weekly paclitaxel in combination with carboplatin in a larger population of patients with advanced NSCLC complicated by IIPs.

Materials and methods

Study design

Chemotherapy- or radiotherapy-naïve patients with pathologically confirmed, inoperable cases (including stage IIIA cases which in principle are candidate for radical radiotherapy, but were judged to be inoperable by taking the risk of IIPs) or post-operative recurrent NSCLC with IIPs who were out of indication for radical radiotherapy due to complication of IIPs at Nippon Medical School Hospital were enrolled in this study. Patients with unstable and acute/subacute IIPs, those receiving oxygen inhalation or using immunosuppressive drugs except for steroids, and those with evident connective tissue disease, patients with past history of AE were excluded. Histological types of lung cancer were defined according to the World Health Organization Classification. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1, estimated life expectancy > 3 months, measurable lesion, and adequate bone marrow, hepatic, and renal functions. All enrolled patients provided written informed consent.

Idiopathic interstitial pneumonias were classified into two groups: a usual interstitial pneumonia (UIP) pattern and a non-UIP pattern. The UIP pattern group consisted of patients with histologically or clinically diagnosed IPF, whereas all remaining patients were defined as the non-UIP pattern group. The diagnosis of IPF was made according to the criteria of the American Thoracic Society/European Respiratory Society [5]. UIP was determined by histological evaluation of open-lung or transbronchial lung biopsy specimens. In the absence of histological diagnosis, at least 2 board-certificated pulmonologists reviewed the computed tomography (CT) scans. The diagnosis of the UIP pattern was based on findings from a high-resolution CT (HRCT) scan of the chest and other clinical features. Typical chest CT findings of the UIP pattern included basal predominant, subpleural reticular abnormality with traction bronchiectasis, honeycomb cysts, and absence of atypical features of IPF such as peribronchovascular nodules, isolated cysts or consolidation [11–13]. The non-UIP pattern was characterized by the presence of basal predominant, non-specific pulmonary fibrosis and/or ground glass opacities, and other infiltrative shadows inconsistent with the UIP pattern. In addition, the presence of other typical clinical features, including bibasilar inspiratory crackles, abnormal findings of pulmonary function tests indicative of restrictive respiratory failure, and increased serum levels of markers of pneumocyte damage [i.e., lactate dehydrogenase (LDH), C-reactive protein (CRP), KL-6, and surfactant protein D (SP-D)], was investigated. All patients had either clinical evidence of IPF or fibrotic non-specific interstitial pneumonia.

AEx of IIPs was defined according to the following criteria [14, 15]: exacerbation of dyspnea within 1 month; newly developed diffuse pulmonary opacities on chest CT and/or chest X-ray; decrease in arterial oxygen tension of more than 10 mmHg under similar conditions; and absence of heart failure or infectious lung diseases. When diagnosis of AEx was uncertain, HRCT, evaluation of cardiac function, and bacteriovirological examination were performed for differential diagnoses. Following the diagnosis of AEx, high-dose steroid therapy with intravenous methylprednisolone, and/or administration of an immunosuppressant was undertaken.

This study was approved by the Institutional Review Board of Nippon Medical School Hospital (Approval number: 220037).

Study treatment

Patients received paclitaxel (100 mg/m^2) on days 1, 8, and 15, and carboplatin (AUC 5.0) on day 1 of each 4-week cycle. Prior to each paclitaxel administration, patients were given 50 mg diphenhydramine orally, and a histamine H2 receptor blocker intravenously along with 8 mg dexamethasone to prevent anaphylactic shock. Treatment was discontinued in the presence of one or more of the following events: disease progression, unacceptable toxicity such as AEx, patient refusal of further treatment, investigator decision to terminate treatment. There was no plan for administration of prophylactic granulocyte colony-stimulating factor.

Statistical analyses

The primary endpoint of this study was the incidence of treatment-related AEx. Secondary endpoints were toxicity, ORR, progression-free survival (PFS) and OS. Based on the previous reports [10], the threshold incidence rate and expected onset rate were set at 30% and 10%, respectively. The number of cases calculated under the condition of $\alpha = 0.05$ and $\beta = 0.2$ was 33 cases. Considering the drop-out example, 35 cases were taken. Patients diagnosed with collagen vascular disease-associated interstitial pneumonia (CVD-IP) after enrollment were excluded from the analysis. The evaluation was conducted in compliance with the National Cancer Institute Common Toxicity Criteria Version 3.0 for safety, and the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines [16] for antitumor activity. Based on previous findings [7], AEx occurring within 10 weeks following treatment termination was considered to be related to chemotherapy.

PFS was defined as the period from treatment initiation to the identifiable time of disease progression. Data are presented as mean ± standard deviation (SD). Survival time was defined as the period from treatment initiation until death by any cause. PFS and OS were determined using the Kaplan–Meier method.

Results

Patients' characteristics

A total of 35 Japanese patients (31 males and 4 females) were enrolled between June 2009 and September 2014 (Table 1). Two patients were diagnosed with rheumatoid arthritis and polymyositis-dermatomyositis after registration, thus the AEx/survival analysis was conducted in 33 patients. The median age at the time of diagnosis of lung cancer was 68 years; Almost all patients ($N = 31$; 94%) were current or former smokers. Thirteen patients had histological confirmation of IIPs. Sixteen patients were clinically or histologically confirmed as having IPF, while 13 patients had stage IV disease or post-operative recurrence. Histologically, squamous cell carcinoma and adenocarcinoma were observed in 14 and 13 patients, respectively. There were no patients receiving steroid. A median of 4 cycles of treatment was administered (range 1–6 cycles) and the vast majority of patients ($N = 26$; 78.8%) received at least three cycles.

Baseline blood data are shown in Table 1. The median of arterial oxygen tension was 84 mmHg (range 61.7–118.7) at rest. In the pulmonary function test, the percentage of predicted vital capacity (% VC) was 89% (range 63.1–165.5), and the percentage of predicted diffusing capacity of the lungs for carbon monoxide (% DLCO) was 70% (range 43.0–121.7).

Table 1 Characteristics of all patients registered in this study

Number of patients	35
Gender	
Male	31
Female	4
Age (years)	
Median (range)	68 (55–78)
Smoking history	
Current or former smoker	33
Never	2
Smoking index (packs/year)	
Median (range)	57 (0–175)
PS (ECOG)	
0	18
1	17
Stage	
IIIA	15
IIIB	7
IV	10
Recurrent	3
Histology	
Squamous cell	16
Adenocarcinoma	13
Undifferentiated	6
IP classification	
Idiopathic	33
Collagen vascular disease-associated	2
IIPs pattern (histological diagnosis)	
UIP	18 (5)
Non-UIP	17 (9)
IIPs severity	
I	23
II	9
III	3
IV	0
PaO_2 (mmHg)	
Median (range)	84 (61.7–118.7)
%VC (predicted) (%)	
Median (range)	89 (63.1–165.5)
%DLCo (predicted) (%)	
Median (range)	70 (43.0–121.7)

PS performance status, *ECOG* Eastern Cooperative Oncology Group, *IP* interstitial pneumonia, *IIPs* idiopathic interstitial pneumonias, *UIP* usual interstitial pneumonia, *IIPs Severity* based on the disease severity in IPF by JRS classification

Table 2 Incidence of acute exacerbation

Number of patients	33
Acute exacerbation	
First-line treatment-related	4 (12.1%, 95% CI 3.4–28.2)
(to death)	0
Second-line treatment-related	0
Third-line treatment-related	1
(to death)	1
Unrelated to treatment	1
(to death)	1
Total number of acute exacerbations	6 (18.2%)

Acute exacerbation

AEx related to paclitaxel with carboplatin therapy was observed in 4 patients (12.1%, 95% confidence interval 3.4–28.2%) (Table 2). The clinical background of the 6 patients who developed treatment-related AEx during first-line chemotherapy (carboplatin plus paclitaxel) or AEx unrelated to treatment during the observation period is summarized in Table S2. All 4 patients were clinically diagnosed with IIPs. Of those, 3 patients were diagnosed with IPF. The severity of the IIPs was I ($PaO_2 \geq 80$ mmHg at rest) and II ($70 \leq PaO_2 \leq 80$ mmHg at rest) in 1 and 3 patients, respectively, applying the Japanese disease severity classification (JSC) for IPF [17]. All patients received corticosteroid therapy and 1 patient received intravenous cyclophosphamide after steroid pulse therapy. All patients improved after therapy. There were no fatalities due to the occurrence of AEx.

Toxicities

Treatment-related adverse events other than AEx are shown in Table 3. The most common hematological grade 3 or 4 adverse event was neutropenia ($N = 23$; 69.7%), and febrile neutropenia was observed in 5 patients (15.2%). The most common non-hematological adverse events were nausea and anorexia, and were mild in severity. Either adverse events were reversible.

Table 3 Treatment-related adverse events excluding acute exacerbation

Toxicity	Grade 2	Grade 3	Grade 4	Grade 3 or 4 (%)
Neutropenia	3	17	6	23 (69.7)
Anemia	2	4	0	4 (12.1)
Thrombocytopenia	0	1	0	1 (3.0)
Febrile neutropenia	0	3	2	5 (15.2)
Nausea	3	2	0	2 (6.1)
Anorexia	1	2	0	2 (6.1)

Table 4 Objective response to treatment

Number of patients	33
Objective response	
CR + PR	23
SD	8
PD	1
NE	1
Overall response rate (%)	69.7 (95% CI 51.3–84.4%)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

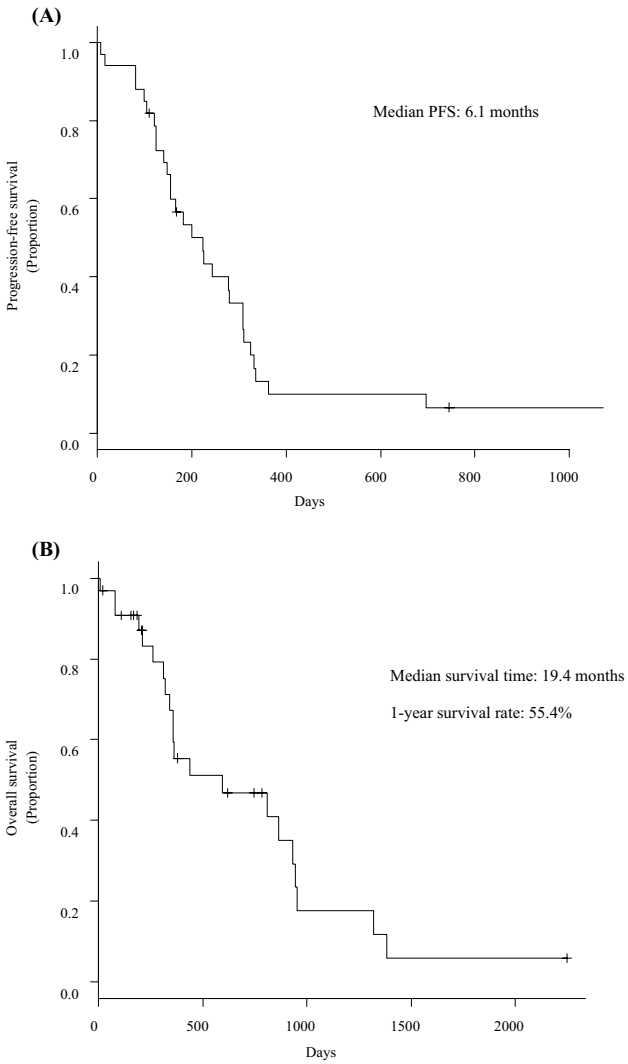

Fig. 1 **a** Progression-free survival (PFS) and **b** overall survival (OS). Vertical bars indicate censored cases at the data cutoff point. The median PFS, median survival time (MST) and 1-year survival rate were 6.3 months, 19.8 months and 55.4%, respectively

Treatment efficacy

Table 4 shows the antitumor effect of this treatment. The ORR and DCR were 69.7% and 93.9% respectively, comprising 23 partial responses and 8 stable disease. Progressive disease were observed in 1 patient. The median PFS was 6.3 months. The median survival time was 19.8 months, and 1-year survival rate was 55.4% (Fig. 1).

Subsequence chemotherapy

Sixteen out of 33 patients (48%) with recurrent disease were administered second-line treatment. The ORR of all regimens was 31%, and there were no cases of AEx related to second-line treatment. The regimens and ORR are shown in Table 5. Twelve patients out of 16 patients (75%) were rechallenged with paclitaxel containing regimen as second-line treatment. The rechallenge group had an ORR of 50% and no cases of AEx.

Discussion

This is the prospective study confirming the safety of a specific cytotoxic chemotherapy regimen for the treatment of patients with lung cancer complicated by IIPs.

The incidence of AEx was 12.1% in this study. The frequency in this study is higher than in the previous pilot study investigating this combination therapy [10]. However, the cumulative incidence of AEx related to cytotoxic chemotherapy ranges from 20 to 28% [7–9]. The 14–21% of IPF patients develop AEx during the natural course [18–21]. In Japan, death related to AEx of IPF was reported as the first cause of mortality (40%) [22]. In the current study, there were no fatalities caused by AEx, suggesting that carboplatin combined with weekly paclitaxel can be employed safely for the treatment of patients with lung cancer complicated by IIP.

Chemotherapy using carboplatin combined with weekly paclitaxel is recognized as a standard treatment for advanced NSCLC, The clinical efficacy and safety have been reported in numerous studies [23–25]. The ORR ranged from 32 to 45%, and the median OS ranged from 12 to 14 months were shown. Moreover, weekly paclitaxel has shown good safety and efficacy in high-risk patients such as the elderly and those who have received previous treatment [24–26]. In the current study, an ORR of 69.7% and a median PFS of 7.5 months were observed. These findings are comparable to the results of a randomized phase III trial involving Japanese patients without IIPs (ORR: 32.4%; median PFS: 4.5 months) [26]. We have included stage IIIA cases in this study, but compared to best supportive care, there are still an advantage of prolonged survival.

This study has several limitations. Firstly, this was a single-arm, single-institution study. The performance status was limited to PS 0 or 1. Most of the diagnoses of IIPs were based on CT findings instead of histologic diagnosis. The severity of IIPs was limited to mild in this patient population. Second, the recruitment of 35 patients meeting the strict inclusion criteria of this study resulted in a prolonged duration of this investigation. In the meantime, the superiority of the combination of carboplatin + nab-paclitaxel and carboplatin + paclitaxel + bevacizumab to carboplatin + paclitaxel has been demonstrated and the regimen has

Table 5 Second- and third-line chemotherapy regimens

Regimen	*N* = 33	ORR (%)	DCR (%)	Acute exacerbation	Death
Second line	16 (48%)				
PTX	12				
CBDCA + PTX	5	20	40	0	0
CBDCA + nabPTX	2	50	100	0	0
CBDCA + PTX + BEV	3	100	100	0	0
nabPTX	2	0	50	0	0
CDDP + S-1	1	0	100	0	0
PEM	1	0	0	0	0
DTX	1	0	0	0	0
S-1	1	0	0	0	0
Third line	3 (9%)				
CBDCA + PTX	1	0	100	0	0
CBDCA + nabPTX	1	100	100	1	1
CBDCA + DTX	1	0	0	0	0

ORR overall response rate, *DCR* disease control rate, *CBDCA* carboplatin, *PTX* paclitaxel, *nabPTX* nab-paclitaxel, *BEV* bevacizumab, *CDDP* cisplatin, *PEM* pemetrexed, *DTX* docetaxel

become a standard treatment option. In conclusion, we were able to confirm the feasibility of weekly paclitaxel combined with carboplatin for advanced NSCLC patients with IIP and appeared to be more safe than suggested by the previous reports. In addition, as there are newer standard treatment, further investigation is needed.

Acknowledgements This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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