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Is fourth-line chemotherapy routine practice in advanced non-small cell lung cancer?

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ABSTRACT

Background: Despite advances in palliative chemotherapy, patients with advanced non-small cell lung cancer (NSCLC) eventually experience disease progression during or after completion of first-line chemotherapy, which requires salvage therapy. Second- or third-line therapy in selected patients is recommended in the current guidelines. Although fourth-line therapy is often performed in daily practice in some countries, there are few reports about the clinical benefits of fourth-line therapy.
Patients and methods: A retrospective review was conducted on 383 patients who underwent at least first-line palliative chemotherapy for advanced NSCLC (stage IV or stage IIIB/recurrent disease unsuitable for definitive local therapy). Overall survival (OS) and clinicopathological characteristics were analyzed according to the lines of chemotherapy as well as for all study patients.
Results: The median OS for all patients after the initiation of first-line therapy was 11 months. The median OS for patients who received fourth- or further-line therapy (77 patients) was longer than that of patients who received third- or lesser-line therapy (27 versus 9 months, $p < 0.0001$). In multivariate analysis, fourth- or further-line therapy was independently associated with favorable OS (hazard ratio: 0.44, 95% confidence interval: 0.34–0.57, $p < 0.0001$) along with recurrent disease, female, age <70 years, and ECOG performance status (PS) 0 or 1. Median OS after the start of fourth-line therapy was 9 months. Good PS (ECOG PS 0, 1) at the initiation of fourth-line therapy (10 versus 2 months, $p < 0.0001$) and disease control (10 versus 7 months, $p = 0.011$) after first-line therapy were associated with favorable OS in univariate analysis, while poor PS (ECOG PS $\geq$2) was an independent prognostic factor for poor outcome ($p < 0.0001$).
Conclusion: The present study suggests that advanced NSCLC patients with good PS after progression from third-line therapy could be considered as reasonable candidates for fourth-line therapy in clinical practice.

1. Introduction

Lung cancer is the most common malignancy in many countries, and the first leading cause of cancer-related death in men and women in Korea [1,2]. Approximately 87% of newly diagnosed cases are non-small cell lung cancer (NSCLC), while around 70% of patients with NSCLC are diagnosed with advanced disease [3,4]. Despite advances in palliative chemotherapy, the outcome of advanced NSCLC is still very poor, with a median survival of 8–12 months [4,5].

The standard first-line palliative chemotherapy for patients with advanced NSCLC is platinum and third-generation agent doublet combination [5]. Despite a modest survival benefit, every patient experiences disease progression during or after completion of first-line therapy that requires salvage therapy. Based on results from phase III trials that demonstrated overall survival (OS) improvement, docetaxel, pemetrexed, and epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib or erlotinib are recommended as second-line therapy [6–8]. Although no strong evidence supports the efficacy of third-line chemotherapy except erlotinib, third-line therapy in selected patients has

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Table 1
Patients characteristics.

Characteristics	Total *N* (%)	1,2,3rd line CTx *N* (%)	≥4th line CTx *N* (%)	*p* value
Gender				
Female	142 (37.1)	109 (35.6)	33 (42.9)	0.291
Male	241 (62.9)	197 (64.4)	44 (57.1)	
Age (years)				
<70	319 (83.3)	251 (82.0)	68 (88.3)	0.232
≥70	64 (16.7)	55 (18.0)	9 (11.7)	
Smoking				
No	149 (38.9)	115 (37.6)	34 (44.2)	0.298
Yes	234 (61.1)	191 (62.4)	43 (55.8)	
PS (ECOG)				
0, 1	344 (89.8)	274 (89.5)	70 (90.9)	0.796
2	34 (8.9)	27 (8.8)	7 (9.1)	
3, 4	5 (1.3)	5 (1.6)	0 (0.0)	
Histology				
Adenocarcinoma	272 (71.0)	206 (67.3)	66 (85.7)	0.009
Squamous	68 (17.8)	62 (20.3)	6 (7.8)	
Others	5 (1.3)	4 (1.3)	1 (1.3)	
NOS	38 (9.9)	34 (11.1)	4 (5.2)	
Stage				
IIIB	14 (3.7)	14 (4.6)	0 (0.0)	0.146
IV	332 (86.7)	263 (85.9)	69 (89.6)	
Recurrent disease	37 (9.7)	29 (9.5)	8 (10.4)	
Brain metastasis[a]				
No[b]	326 (85.1)	256 (83.7)	70 (90.9)	0.150
Yes[c]	57 (14.9)	50 (16.3)	7 (9.1)	
1st line CTx				
Doublet	298 (77.8)	234 (76.5)	64 (83.1)	0.224
Single	85 (22.2)	72 (23.5)	13 (16.9)	

N, number; CTx, chemotherapy; PS, performance status; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.
[a] Including cases diagnosed at the initiation of first-line chemotherapy only.
[b] Including not evaluated cases.
[c] Including one leptomeningeal carcinomatosis case without definitive brain metastasis (the only leptomeningeal metastasis case).

recently been accepted as a reasonable therapeutic option under the recommendations of the ASCO and ESMO guidelines [8–11].

However, the role of additional chemotherapy for patients with progressive disease after third-line treatment remains unclear without prospective or randomized studies specifically designed to prove the benefits of fourth-line treatment. Nonetheless, fourth- and further-line chemotherapy has been performed often in daily clinical practice in some countries including Korea [12–15]. Therefore, to assist oncologists in identifying patients who will benefit from fourth-line therapy after progression from third-line therapy, we retrospectively analyzed the outcomes and clinicopathological characteristics of patients with advanced NSCLC who received fourth- or further-line chemotherapy.

2. Patients and methods

2.1. Study population

We retrospectively identified all patients with advanced NSCLC who initiated first-line palliative chemotherapy between January 2002 and December 2011 at our institution. The criteria for eligibility were histologically or cytologically documented NSCLC, either stage IV according to the 7th edition of the American Joint Committee on Cancer (AJCC) [16] or stage IIIB/recurrent disease unsuitable for definitive local therapy. We excluded patients with locally advanced or recurrent NSCLC who underwent palliative chemotherapy due to progression after initial definitive chemoradiotherapy or radiotherapy. Patients who had started first-line chemotherapy at other hospitals during this period and received further therapy at our institution were included if adequate chemotherapy information was available. This research protocol was approved by the Institutional Review Board of Ajou University Hospital.

2.2. Clinical review

A retrospective review of the clinical information of eligible patients was performed. Data on the patients including patient characteristics (age, gender, smoking history, performance status (PS) based on the Eastern Cooperative Oncology Group (ECOG) performance scale, histology, clinical stage at diagnosis, brain metastasis); chemotherapy regimen; total chemotherapy lines; objective response according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [17], and survival information were collected.

2.3. Statistical analysis

Overall survival (OS) was calculated using the Kaplan–Meier Method. OS was defined as the time from the start day of the first- or fourth-line chemotherapy to death. Data on the survivors were censored at the last follow-up. The differences between the survival curves were analyzed by using the log-rank test. Fisher's exact test was used to compare different groups for categorical variables. The Cox proportional-hazards regression model was used to determine the joint effects of several variables on survival. Factors with p values <0.1 in the univariate analysis were included in the Cox proportional-hazards regression model. All statistical analyses were performed two-sided with SPSS for Windows 13.0 software.

3. Results

3.1. Patient characteristics

A total of 389 patients who underwent at least first-line palliative chemotherapy for advanced NSCLC were identified. Among them, four patients with inadequate chemotherapy