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Efficacy and Safety of Continuing Bevacizumab beyond Disease Progression plus Docetaxel in Patients with Non-Small Cell Lung Cancer: A Retrospective Analysis

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Abstract

Background: Bevacizumab-based chemotherapy has been shown to extend progression-free survival (PFS) of lung cancer, but its effect on overall survival (OS) remains unclear. However, bevacizumab beyond disease progression (BBP) significantly improved OS in patients with metastatic colorectal cancer. Methods: Therefore, we retrospectively analysed 22 patients with non-small cell lung cancer (NSCLC) who were treated with docetaxel plus BBP at the Department of Thoracic Oncology, Kansai Medical University Hirakata Hospital, between November 2009 and March 2013. Results: The response rate was 31.8% and the disease control rate was 86.4%. The median PFS was 4.5 months (95% confidence interval [CI], 2.5 - 8.7 months) and the median OS was 17.2 months (95% CI, 8.5 - 25.9 months). Grade 3 and 4 adverse events included leukocytopenia (68.2%), neutropenia (77.3%), fatigue (9.1%), proteinuria (9.1%), febrile neutropenia (4.5%), anemia (4.5%), and anorexia (4.5%). Conclusion: Docetaxel plus BBP was found to be generally well tolerated and effective.

Keywords

Bevacizumab beyond Disease Progression, NSCLC, Second-Line Chemotherapy, Docetaxel

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1. Introduction

Non-small cell lung cancer (NSCLC), primarily including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, accounts for approximately 80% - 85% of all lung cancers, and approximately two-thirds of NSCLC patients are found to have advanced-stage disease at diagnosis. The standard of care for the initial treatment of these patients is a platinum-based, two-drug chemotherapy. However, its therapeutic effect is limited and the prognosis of patients with advanced NSCLC remains poor.

Recently, new treatment strategies for NSCLC have been introduced. One of these is based on targeting driver mutations such as the anaplastic lymphoma kinase rearrangement and the epidermal growth factor receptor mutation. Other strategies include the use of the folate antimetabolite pemetrexed, the administration of maintenance therapy, and the disruption of neo-angiogenesis using anti-vascular endothelial growth factor (VEGF) antibodies such as bevacizumab. The latter is a humanized monoclonal antibody that inhibits angiogenesis and results in tumour necrosis and the inhibition of metastasis. A randomized phase II study of bevacizumab combined with chemotherapy showed promising results and suggested that this was suitable for non-squamous NSCLC patients in terms of its acceptable serious toxicity profile [1]. Two randomized phase III studies and a randomized phase II study were subsequently performed in Japan in order to compare chemotherapy plus bevacizumab with chemotherapy alone for the initial treatment of advanced non-squamous NSCLC [2]-[4]. However, Eastern Cooperative Oncology Group (ECOG) 4599 was the first phase III study that showed a statistically significant benefit in terms of both overall survival (OS) and progression-free survival (PFS) with bevacizumab in combination with carboplatin plus paclitaxel compared with carboplatin plus paclitaxel alone in NSCLC [2]. In contrast, both the Avastin in Lung trial (AVAiL), which evaluated cisplatin plus gemcitabine with or without bevacizumab, and a Japanese randomized phase II study, which evaluated carboplatin plus paclitaxel with or without bevacizumab, demonstrated a significantly longer PFS in the bevacizumab arm, but there was no significant difference in OS [3] [4]. Although the combination of bevacizumab and carboplatin plus paclitaxel was established as a standard of care for non-squamous NSCLC patients based on the ECOG study results, many oncologists doubted whether bevacizumab was truly beneficial in the treatment of NSCLC because bevacizumab-containing regimens did not prolong OS in other studies.

Recently, the administration of bevacizumab beyond disease progression (BBP) has been of interest. Preclinical studies have shown rapid reconstruction of tumour blood vessels after the discontinuation of angiogenesis inhibitors [5] [6] and have suggested that permanent vascularization inhibition could maintain antitumour efficacy. Indeed, a randomized phase III study demonstrated that the maintenance of VEGF inhibition with bevacizumab as BBP in combined second-line chemotherapy significantly improved OS in patients with metastatic colorectal cancer [7]. This approach has also been under consideration for non-squamous NSCLC, but until now, there has been no evidence to support the administration of BBP in patients with this malignancy. Therefore, we retrospectively analysed the efficacy and safety of docetaxel plus BBP in patients with non-squamous NSCLC who showed disease progression after first-line treatment with bevacizumab.

2. Materials and Methods

This was a retrospective study of 22 advanced non-squamous NSCLC patients who were treated with docetaxel plus bevacizumab as second-line therapy after disease progression following first-line treatment with bevacizumab plus platinum-based doublet therapy at the Department of Thoracic Oncology, Kansai Medical University Hirakata Hospital, between November 2009 and March 2013. From the patient charts, we retrieved the following data: age, gender, disease stage, histology, complete blood count, liver and kidney function test results, computed tomography/magnetic resonance imaging scans of the whole body and brain, and the epidermal growth factor receptor status.

Objective tumour responses were evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1 [8], by each attending physician. Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events, version 4.0 [9]. PFS and OS were estimated using the Kaplan-Meier method.

3. Results

3.1. Patient Characteristics

Twenty-two non-squamous NSCLC patients were treated with docetaxel plus BBP as second-line therapy. The

patient characteristics are listed in **Table 1**. Sixteen patients (72%) were male and 6 (28%) were female, and their median age was 63 years (range, 40 - 70 years). Three patients (13%) had an ECOG performance status of 0, 16 (74%) had an ECOG performance status of 1, and 3 (13%) had an ECOG performance status of 2. One patient (7%) had stage IIIB disease, 19 (86%) had stage IV disease, and 2 (9%) had postoperative recurrence. All of the patients had adenocarcinoma. As first-line chemotherapy, 21 patients were treated with carboplatin, pemetrexed, and bevacizumab, and 1 (5%) patient was treated with cisplatin, gemcitabine, and bevacizumab. The median course of docetaxel plus BBP was 7 courses (range, 1 - 22).

3.2. Efficacy

Of the 22 patients, 7 (31.8%) achieved a partial response (PR), resulting in a response rate (RR) of 31.8%. The other 12 patients (54.6%) achieved stable disease (SD) as their best response to therapy, resulting in a disease control rate (DCR) of 86.4% (**Table 2**). The median PFS was 4.5 months (95% confidence interval [CI], 2.5 - 8.7 months) (**Figure 1**), and the median OS was 17.2 months (95% CI, 8.5 - 25.9 months) (**Figure 2**).

3.3. Safety

All AEs are listed in **Table 3**. AEs of grade 3 or higher were observed in 18 patients (81.8%). Grade 3 and 4 haematological AEs included leukocytopenia (68.2%), neutropenia (77.3%), febrile neutropenia (4.5%) and anemia (4.5%), and grade 3 and 4 non-haematological AEs included fatigue (9.1%), proteinuria (9.1%), and

Table 1. Patient characteristics.

n = 22	Patients	
	No.	%
Median age (years)	63	
Range (years)	40 - 70	
Gender		
Male	16	72
Female	6	28
ECOG PS		
0	3	13
1	16	74
2	3	13
3 - 4	0	0
Disease stage		
IIIB	1	5
IV	19	86
Postoperative recurrence	2	9
Histology		
Adenocarcinoma	22	100
Previous chemotherapy		
CBDCA + Pem + Bev	21	95
CDDP + Gem + Bev	1	5

CBDCA: carboplatin; Pem: pemetrexed; Bev: bevacizumab; Gem: gemcitabine.

Table 2. Response to treatment.

Response	n (%)
CR (%)	0 (0)
PR (%)	7 (31.8)
SD (%)	12 (54.6)
PD (%)	3 (13.6)
RR (CR + PR)	31.8%
DCR (CR + PR + SD)	86.4%

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; RR: response rate; DCR: disease control rate.

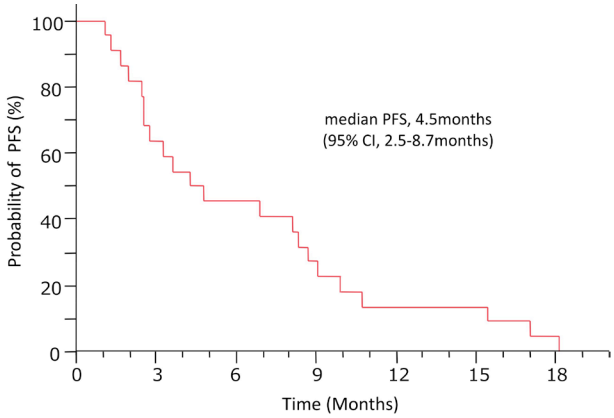

Figure 1. Progression-free survival.

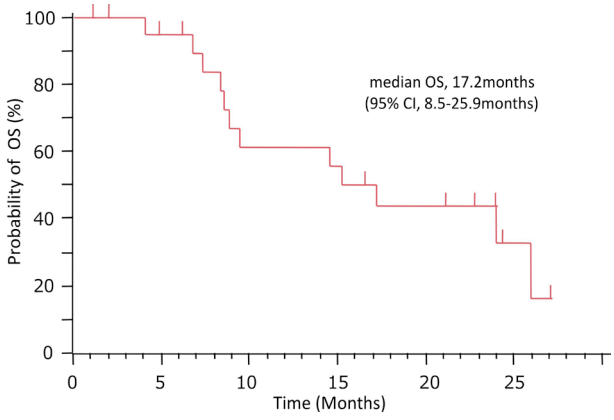

Figure 2. Overall survival.

anorexia (4.5%). No patient experienced hypertension or venous thrombosis of grade 3 or higher severity (**Table 3**).

4. Discussion

Docetaxel or pemetrexed monotherapy are the current standard chemotherapies for non-squamous NSCLC patients who have previously failed platinum-containing chemotherapy. In phase III studies by Shepherd *et al.* and Fossella *et al.*, docetaxel for pretreated NSCLC patients with a good PS increased the 1-year survival rate by 10% to 20% compared with treatment with ifosfamide, vinorelbine, or best supportive care alone [10] [11]. In

Table 3. Adverse events.

	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytopenia	3 (13.6%)	5 (22.7%)	6 (27.3%)	9 (40.9%)
Neutropenia	2 (9.1%)	3 (13.6%)	8 (36.4%)	9 (40.9%)
Anemia	6 (27.3%)	4 (18.2%)	1 (4.5%)	0
Thrombocytopenia	0	0	0	0
Fatigue	12 (54.5%)	4 (18.2%)	2 (9.1%)	0
Anorexia	14 (63.6%)	3 (13.6%)	1 (4.5%)	0
Nausea	11 (50.0%)	0	0	0
Mucositis Oral	9 (40.9%)	0	0	0
Constipation	4 (18.2%)	0	0	0
Liver damage	1 (4.5%)	0	0	0
Proteinuria	3 (13.6%)	3 (13.6%)	2 (9.1%)	0
Fever	3 (13.6%)	0	0	0
Infection	3 (13.6%)	0	0	0
Febrile neutropenia	0	0	0	1 (4.5%)
Venous thrombosis	0	0	0	0
Bleeding	0	0	0	0
Alopecia	7 (31.8%)	0	0	0
Pneumonitis	0	0	0	0

these studies, the median time to progression was 8.5 - 10.6 weeks, the RR was 6.7% - 7.1%, and the 1-year survival rate was 32% - 37%. However, in a phase III randomized controlled trial, second-line pemetrexed monotherapy resulted in an RR of 9.1%, a median PFS of 2.9 months, and a median OS of 8.3 months [12]. This study also showed that treatment with pemetrexed resulted in clinically equivalent efficacy with significantly fewer side effects compared to docetaxel in the second-line treatment of patients with advanced NSCLC.

Several clinical studies of combined doublet chemotherapy for NSCLC as second-line treatment have also been conducted. In a meta-analysis of second-line single-agent chemotherapy compared with combination chemotherapy for advanced NSCLC, the latter was found to have significantly increased the response rate and PFS, but was more toxic and did not improve OS compared to single-agent therapies [13]. Thus, single-agent monotherapy is still the standard second-line chemotherapy for NSCLC.

Recently, there has been growing interest in treatment using BBP. Preclinical studies have shown that rapid reconstruction of tumour blood vessels occurs after discontinuation of angiogenesis inhibitors [5] [6] and have suggested that permanent vascularization inhibition maintains antitumor efficacy. In fact, a randomized phase III study demonstrated that maintenance of VEGF inhibition with bevacizumab as BBP in combined second-line chemotherapy significantly improved OS in metastatic colorectal cancer [7]. Similarly, BBP is also expected to be beneficial in other cancers.

In this retrospective analysis, which is also the first analysis of BBP in NSCLC, docetaxel plus BBP resulted in a good response rate and longer PFS and OS. In the DELTA study, which was a phase III study to compare erlotinib and docetaxel in the treatment of Japanese pretreated non-squamous NSCLC patients, docetaxel resulted in a response rate of 17.9%, a median PFS of 3.2 months, and a median OS of 12.2 months [14], which is an improvement compared to previous studies. Our findings suggested the possibility of superior therapeutic results compared to the DELTA study and other previous studies (**Table 4**, **Table 5**), although there is a possibility of selection bias arising from the small sample size and retrospective nature of our analysis. To assess the

Table 4. Efficacy of second-line, post-progression treatment in this and previous studies.

	This analysis n = 22 (DTX + Bev)	DELTA [14] n = 301 (DTX)	Hanna *et al.* [12] n = 571		Roszkowski *et al.* [17] n = 207 (DTX)
			DTX	Pem	
RR	31.8%	17.9%	8.8%	9.1%	13.1%
DCR	86.4%	77.2%	55.2%	54.9%	-
mPFS (months)	4.5	3.2	2.9	2.9	3.2
mOS (months)	17.2	12.2	7.9	8.3	6.0

RR: response rate; DCR: disease control rate; mPFS: median progression-free survival; mOS: median overall survival; DTX: docetaxel; Bev: bevacizumab; Pem: pemetrexed.

Table 5. Grade 3 - 4 adverse events comparing this analysis versus DELTA study.

	This analysis n = 22 (DTX + Bev)	DELTA [14] n = 301 (DTX)
Leukocytopenia	68.2%	63.6%
Neutropenia	77.3%	79.5%
Febrile neutropenia	4%	15.2%
Anemia	4%	7.9%
Thrombocytopenia	0%	2%
Fatigue	9%	4.6%
Nausea	0%	3.3%
Liver damage	0	0.7%
Pneumonitis	0%	2%

DTX: docetaxel; Bev: bevacizumab.

efficacy and safety of chemotherapy plus BBP for patients who had previously failed platinum-containing chemotherapy, a further prospective study is required. Indeed some prospective studies of BBP, for example, West Japan Oncology Group 5910L and AvaALL (MO22097) [15] [16], are already underway.

5. Conclusion

In conclusion, docetaxel plus BBP showed good efficacy and safety in patients with non-squamous NSCLC who showed disease progression after first-line treatment with bevacizumab in this retrospective analysis. It is possible, therefore, that this regimen will become a standard second-line treatment for non-squamous NSCLC.

Conflicts of Interest

There are no conflicts of interest to declare.

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