

Long-term Progression-free Survival With Pemetrexed Plus Bevacizumab in NSCLC Patients

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Abstract. *Background/Aim:* Pemetrexed (PEM) and bevacizumab (BEV) are commonly used in combination as second or subsequent line regimens and maintenance therapy after platinum + PEM + BEV therapy for advanced non-small cell lung cancer (NSCLC). Median progression-free survival (PFS) for PEM + BEV has been reported to be less than six months in both clinical trials and clinical practice, but in clinical practice, we found that some patients demonstrate long-term PFS. Furthermore, there is a paucity of clinical practice data on whether long-term administration of PEM + BEV causes renal dysfunction. This study aimed to clarify these aspects in clinical practice. *Patients and Methods:* A retrospective review of patients with advanced NSCLC treated with PEM + BEV between September 2011 and June 2022 at four hospitals was conducted. Long-term PFS in PEM + BEV therapy was defined as ≥ 12 months. *Results:* During the study period, 109 patients received PEM + BEV treatment. Of them, 42 (38.5%) achieved long-term PFS ≥ 12 months. No significant differences in patient characteristics were found between patients with PFS ≥ 12 months and < 12 months,

except for 'relapse after resection'. Univariate and multivariate analysis showed that the favorable factor for PFS was 'relapse after resection'. With regard to influence on renal function of PEM + BEV therapy, no significant difference was found before and after PEM+BEV therapy between these two groups. Conclusion: NSCLC patients commonly achieved long-term PFS with PEM + BEV therapy with no observed effects on renal function.

Pemetrexed (PEM) is an antimetabolite antineoplastic agent that exerts its antitumor effect by inhibiting DNA synthesis via simultaneously inhibiting multiple folate-metabolizing enzymes. Bevacizumab (BEV) is an antivascular endothelial growth factor receptor-2 (anti-VEGFR2) monoclonal antibody (1, 2). BEV suppresses tumor growth by preventing VEGF from binding to VEGFR2 and activating downstream angiogenic signals (1, 2). During the past two decades, platinum + PEM + BEV has been a first-line chemotherapy regimen for patients with advanced non-squamous non-small cell lung cancer (NSCLC), due to its effective antitumor effects and mild toxicity. Currently, PEM + BEV combination therapy is widely used for advanced NSCLC as second-line and subsequent therapy or as maintenance therapy after platinum + PEM + BEV therapy (3-9). This combination regimen is widely recognized as a treatment regimen that has a low incidence of difficult-to-manage myelosuppression, peripheral neuropathy, and febrile neutropenia (3-9). Despite these favorable evaluations, the median progression-free survival (PFS) from primary treatment including platinum, or from the start of PEM+BEV in clinical practice was 5.7 to 7.5 months (3-7) and 6.0-7.36 months (8, 9), respectively.

Although NSCLC patients with long-term PFS on PEM+BEV therapy have been rarely reported (10), there are patients undergoing long-term PEM+BEV therapy in real-world clinical practice. In our two decades of practice, we

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have regularly observed patients with a long-term PFS with this treatment regimen. Therefore, we performed a retrospective study with the aim of clarifying: 1) the percentage of patients with long-term PFS, and 2) the characteristics of patients who have long-term PFS. Favorable factors associated with long-term PFS with PEM + BEV therapy were investigated in this study. Since there has been some concern about the deterioration of renal function due to long-term administration of these drugs (11, 12), we also investigated renal function of patients who received long-term administration of these drugs.

Patients and Methods

Patients. The medical records of all patients diagnosed with NSCLC and treated with PEM+BEV for any treatment line between September 2011 and June 2022 at four tertiary hospitals in Japan (Mito Medical Center, University of Tsukuba-Mito Kyodo General Hospital, Ryugasaki Saiseikai Hospital, and Seinan Medical Center Hospital) were investigated. Using the World Health Organization classification, NSCLC was diagnosed pathologically. Prior to the initiation of any anticancer therapy, clinical staging was determined with tumor node metastasis staging (TNM Classification, eighth edition) (13) using computed tomography/magnetic resonance imaging of the head, ultrasonography/computed tomography of the abdomen, and bone scans. Patient information such as age, sex, Eastern Cooperative Oncology Group score for performance status, histopathology, disease stage, programmed death-ligand 1 expression, objective tumor response, and survival were extracted from medical records. Driver mutations including epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements were surveyed. Tumor response was categorized as complete response, partial response, stable disease, or progressive disease according to the Response Evaluation Criteria in Solid Tumors (version 1.1) (14). Adverse events were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) (15).

Definition of long-term PFS for PEM+BEV. Most of the reported 'long-term PFS' relate to PFS for first-line chemotherapy (16). There are few reports on PFS in second- or later-line treatment of NSCLC (17-20). PEM+BEV are usually delivered as second- or later-line chemotherapy. As such, this may be the reason we did not find any reports with a search for 'long-term PFS' and this regimen. 'Long-term PFS' was then defined using clinical trial PFS and actual clinical practice, where the median PFS with this regimen was less than 6 months (3-9). Based on these results (3-9) and this study, 'long-term PFS' was defined as a PFS of ≥ 12 months.

Renal function. Renal impairment was assessed by examining changes in blood urea nitrogen (BUN) and creatinine before and after PEM+BEV treatment and comparing a group of patients with PFS of 12 months or more with a group of patients with PFS of less than 12 months. We also investigated the percentage of patients with (+) and (++) proteinuria at the end of PEM+BEV treatment.

Statistical analysis. The chi-square test was used to test proportions. Values with unknown population variance were compared using the nonparametric Mann-Whitney test. Commonly used in cancer therapy,

PFS is defined as the time from initiation of anticancer therapy to progression. PFS of PEM+BEV was calculated according to this definition. Kaplan-Meier curves were used to display PFS. In univariate analysis, the log-rank test was used to compare PFS. Cox's proportional hazards model was used for multivariate analysis. Multivariate analysis was performed using only variables with *p*-values less than 0.2 in univariate analysis. All statistical analyses were performed using SPSS version 23 (IBM Corporation, Armonk, NY, USA). A *p*-value less than 0.05 was considered statistically significant.

Ethics. The present study complied with the ethical guidelines for clinical research issued by the Ministry of Health, Labor, and Welfare of Japan. Written informed consent to participate in a non-interventional retrospective study was obtained from each patient. The Ethical Committee of Mito Medical Center-University of Tsukuba approved this study (no. 20-57).

Results

Patient characteristics. A total of 109 patients with NSCLC diagnosed during the study period received PEM+BEV. Of these, 71 were driver gene-negative and 38 were positive (*EGFR* mutation, 29 patients; *ALK* rearranged mutation, 9 patients). The median PFS for these 109 patients was 8.0 months (range=1.0-78.0 months). Figure 1 shows the specific treatment sequences for these 109 patients. Forty-two patients (38.5%) had PFS ≥ 12 months. Table I shows the characteristics of patients when grouped by their PFS (<12 months and ≥ 12 months). There were no significant differences in age, sex, or histology in these patient groups. Fourteen of the 38 patients positive for a driver gene mutation (36.8%) and 24 of the 71 patients negative for a driver gene mutation (33.8%) had a PFS ≥ 12 months. There was no significant difference between the driver gene positive and negative groups. Twenty-two of the 42 patients (52.4%) with a PFS ≥ 12 months received platinum + PEM + BEV prior to PEM+BEV treatment, and 37 of the 67 patients (55.2%) had a PFS <12 months on the same treatment. There was no significant difference between these two groups (*p*=0.8444). The proportion of patients receiving PEM+BEV as first or second line therapy tended to differ between the two groups (*p*=0.0677), and there was a significant difference in 'relapse after resection' between them (*p*=0.0479).

Favorable factors for long-term PFS. With the aim of identifying favorable factors associated with long-term PFS, univariate and multivariate analysis of clinical characteristics of all 109 patients were performed. Results are shown in Table II. In univariate analysis, only 'relapse after resection' was a significant favorable factor for PFS. In multivariate analysis, only 'relapse after resection' was a significant favorable factor for PFS.

Renal function in PEM+BEV therapy. Table III shows a comparison of renal function before and after PEM+BEV in

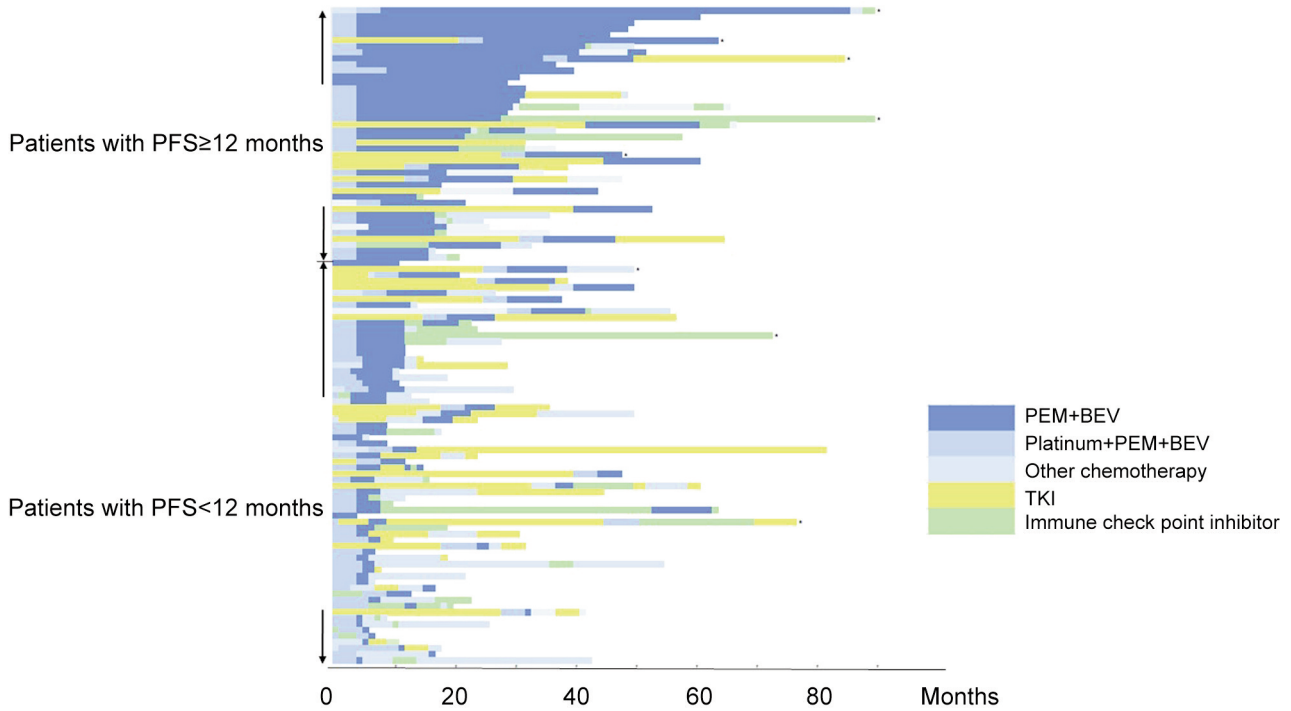


Figure 1. Specific treatment sequences for the 109 patients with non-small cell lung cancer who were treated with pemetrexed+ bevacizumab (PEM+BEV) therapy are shown.

Table I. Characteristics of patients with progression-free survival (PFS) ≥12 months and those with PFS <12 months.

	Patients		p-Value
	Patients with PFS ≥12 months	Patients with PFS <12 months	
Number of patients	42	67	
Sex male:female	24:18	43:24	0.5452
Age, less than 70:70 years or older	28:14	47:20	0.8321
PS, 0-1:2-3	42:0	67:0	0.9999
Pathology, AD:others	40:2	66:1	0.2381
Stage, IIIA-C:IVA-B	12:30	13:54	0.3496
Driver gene, positive:negative	14:28	24:43	0.8387
First line platinum+PEM+BEV: present:absent	22:20	37:30	0.8447
PEM+BEV, -2 nd line: later lines	31:11	37:30	0.0677
Patients with recurrence after resection:	13:29	9:58	0.0479
Patients who had metastases at the time of initial diagnosis			

PS: Performance status; AD: adenocarcinoma; PEM: pemetrexed; BEV: bevacizumab.

patients with PFS <12 months and ≥12 months. Between the two patient groups, there was no statistical difference in changes in BUN or creatinine levels, or percentage of patients with proteinuria at the end of PEM+BEV treatment. There was no patient who had a toxicity criterion of grade 3 (upper limit of normal <3.0, proteinuria >4+).

Discussion

In the present study, we revealed that 39% of NSCLC patients on PEM+BEV therapy had a PFS ≥12 months. Relapse after resection was associated with long-term PFS. In uni- and multivariate analyses of all patients treated with

Table II. Uni- and multivariate analysis of survival from the initiation of pemetrexed and bevacizumab (PEM+BEV) in non-small cell lung cancer patients.

	Univariate analysis (p-value)	Multivariate analysis		
		Odds ratio	95%CI	p-Value
Age, less than 70 years	0.7052			
Sex, female	0.5932			
Stage, IIIA-C	0.1698	1.063	0.636-1.777	0.8159
Pathology, adenocarcinoma	0.9975			
Driver gene, negative	0.5409			
Relapse after resection, yes	0.0112	1.824	1.824-3.143	0.0308
PEM+BEV, -2 nd line	0.2576			

CI: Confidence interval.

Table III. Comparison of renal function before and after pemetrexed+bevacizumab.

	Patients		p-Value
	Patients with PFS ≥12 months	Patients with PFS <12 months	
Pre- and post-treatment differences in BUN median (range) mg/dl	0 (-15.8-10.0)	0.50 (-18.7-14.2)	0.8935
Pre- and post-treatment differences in creatinine, median (range) mg/dl	0.12 (-0.41-0.75)	0.10 (-0.07-0.70)	0.4757
Exacerbation of proteinuria ≥ (+), yes: no	8:34	9:58	0.4321
Exacerbation of proteinuria ≥ (2+), yes: no	6:36	3:64	0.0849
Adverse events ≥ grade 3 present:absent	0:42	0:67	0.9999

BUN: Blood urea nitrogen; PFS: progression-free survival.

PEM+BEV, ‘relapse after resection’ was a favorable factor in the 109 patients. Between patients with PFS <12 months and ≥12 months, there were no statistical differences in changes in BUN or creatinine levels, or the percentage of patients with proteinuria at the end of PEM+BEV treatment. PEM+BEV therapy has been evaluated as one of the standard treatments for second- or later-line regimens, and maintenance therapy after platinum + PEM + BEV therapy for advanced NSCLC (3-9). The median PFS with PEM+BEV has been reported to be around 5-7 months in both clinical trials and clinical practice (3-9). Although there have been very few reports of patients with long-term responses to PEM+BEV (10), we occasionally encountered patients with long-term response in routine clinical practice. Therefore, this study determined the frequency and characteristics of these patients.

With no established definition of long-term PFS in second- and later-line chemotherapy, in this study we defined ‘long-term response’ as having a PFS of 12 months or longer. Under this definition we revealed that there was a considerable number of patients with long-term PFS receiving PEM + BEV therapy. Although we were not able to identify a distinct signature of patients with long-term PFS, we were able to

show that patients with ‘relapse after resection’ are likely to have long-term PFS. Moreover, a certain number of patients that received PEM + BEV therapy were able to demonstrate long-term PFS of 12 months or more. To our best knowledge, no reports have examined the proportion of patients achieving long-term PFS with PEM + BEV therapy and the associated favorable factors in a substantial number of patients. We can only speculate on our observed association of long-term PFS with ‘relapse after resection’. It may indicate a relationship with smaller tumor burden and less spread of lesions. All postoperative patients were monitored regularly with particular attention to ‘relapse after resection’ (21-23). Thus, we speculate that patients with ‘relapse after resection’ were more likely to have a relapse with relatively low tumor burden and a low number of distant metastases.

This study also focused on renal impairment as a side effect of PEM + BEV therapy by comparing patients with a PFS of more than 12 months to those with a PFS of less than 12 months. None of the patients with a PFS ≥12 months or <12 months had grade 3 (upper limit of normal <3.0, proteinuria >4+) toxicity criteria. However, it is possible that renal dysfunction was a consequence, and comparisons between PFS of ≥12 months and <12 months were not sufficient.

In addition to this, our study had some limitations. Data from patients were obtained across four institutions, but this was a retrospective study with a relatively small number of patients with varying background characteristics. It should be noted that our results are preliminary and do not provide final, statistically valid conclusions. *EGFR* mutation and *ALK* rearrangements were examined as driver genes in all patients, however, tests for additional driver genes were performed in a subset of patients as they became newly available during the study period. As a result, most of the driver gene-positive patients carried an *EGFR* mutation or *ALK* rearrangement. In this study, driver mutations were not a significant factor in favor of PFS. However, it might have been better to analyze driver gene-positive patients separately.

The real practice of patients with advanced NSCLC has increased treatment options, including immune checkpoint inhibitors. As a result, longer survival is being achieved. Even in second- or later-line therapies, longer PFS than that observed with current therapies will be provided. In the near future, 'long-term PFS' will be defined even after second-line treatment, and treatment 'quality evaluation' must be required even for the second- or later-line therapy, including PEM+BEV. It is expected that more investigations will be conducted into the long-term response to PEM+BEV therapy. In this sense, our report provides valuable data for later comparison.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

SH, KM, TS, SO, HSaku, and HS designed the study. SH, KM, TS, SO, HSaku, TA and HS collected the data. SH, SO and HS analyzed the data. SH, SO, HS and NH prepared the manuscript. AN, HS and NH supervised the study. All Authors approved the final version for submission.

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