ORIGINAL PAPER

Nagoya J. Med. Sci. **87**. 483–497, 2025
doi:10.18999/nagjms.87.3.483

Influence of renal function on the clinical efficacy of carboplatin plus pemetrexed in patients with non-small cell lung cancer

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ABSTRACT

Pemetrexed, a structural antifolate agent that is eliminated via renal excretion, is commonly used to treat non-squamous non-small-cell lung cancer (NS-NSCLC). Although poor renal function is associated with a high incidence of toxicities, the association of high renal function with chemotherapy efficacy and toxicity remains unknown. We aimed to investigate the effect of renal function on the efficacy and toxicity of carboplatin-pemetrexed chemotherapy in patients with NS-NSCLC. We performed a post-hoc analysis of a prospective observational study of carboplatin-pemetrexed treatment in NS-NSCLC patients. Baseline renal function was calculated using the Japanese estimated glomerular filtration rate (eGFR) formula, and the patients were then divided into two groups based on the eGFR: high-eGFR (eGFR ≥ 80 mL/min/1.73 m^2, N = 162) and low-eGFR (eGFR < 80 mL/min/1.73 m^2, N = 176) groups. Although the response rates in the high- and low-eGFR groups were similar (22.2% vs 23.9%, P = 0.7205), the disease control rate was significantly lower in the high-eGFR group than in the low-eGFR group (75.9% vs 84.7%, P = 0.043). Progression-free survival (PFS) and overall survival (OS) in the high-eGFR group were significantly shorter than those in the low-eGFR group (adjusted hazard ratio for PFS and OS, 1.32 [95% CI, 1.04–1.69; P = 0.0245] and 1.49 [95% CI, 1.15–1.93, P = 0.0023], respectively). The incidence of hematological and

Received: November 16, 2024; Accepted: December 23, 2024
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non-hematological toxicities was lower in the high-eGFR group. In conclusion, a high-eGFR is associated with poor efficacy and mild toxicity of carboplatin-pemetrexed in patients with NSCLC.

Keywords: pemetrexed, glomerular filtration rate, non-small cell lung cancer

Abbreviations:
AUC: area under the blood concentration-time curve
CbP: carboplatin plus pemetrexed
eGFR: estimated glomerular filtration rate
GFR: glomerular filtration rate
NS-NSCLC: non-squamous non-small cell lung cancer
OS: overall survival
PFS: progression-free survival

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in Japan, causing more than 70,000 deaths annually. It is also a major cause of cancer-related deaths in many economically developed countries.[1] Most patients with non-small cell lung cancer (NSCLC) are diagnosed with advanced disease and thus receive palliative treatment consisting of several lines of chemotherapy. Even after the emergence of molecularly targeted drugs and immune checkpoint inhibitors, platinum-doublet chemotherapy remains the standard treatment option for patients with advanced or recurrent NSCLC who lack somatic mutations in driver oncogenes or develop resistance to targeted or immunotherapeutic drugs. Platinum (cisplatin or carboplatin) plus pemetrexed is a common treatment option, particularly for non-squamous (NS)-NSCLC.[2-4] Although cisplatin offers higher efficacy than carboplatin in several meta-analyses[5-7] and a short hydration regimen has been developed for patient convenience,[8] carboplatin is more commonly used because it is less emetogenic and more convenient to administer in an outpatient setting. Carboplatin and pemetrexed (CbP) treatment is also used as first-line therapy for elderly patients with advanced NS-NSCLC.[9-11] Combined treatment with immune checkpoint inhibitors or epidermal growth factor receptor tyrosine kinase inhibitors is currently the standard treatment for NS-NSCLC.[12-16]

Carboplatin is a platinum-based anticancer agent, and its clearance strongly correlates with the glomerular filtration rate (GFR); therefore, the dose of carboplatin is calculated using Calvert's formula based on the target area under the blood concentration-time curve (AUC) and GFR.[17-20] Pemetrexed, a structural antifolate agent, inhibits thymidylate synthase, glycinamide ribonucleotide formyltransferase, and dihydrofolate reductase, which are all folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides.[21] In a phase I trial,[22] the maximum tolerated dose was determined as 600 mg/m^2. However, the dose was reduced to 500 mg/m^2 owing to toxicities (eg, neutropenia and thrombocytopenia) observed in two phase II trials.[23,24] Supplementation of folic acid and vitamin B_{12} is recommended to reduce toxicity, including neutropenia.[25] The elimination of pemetrexed is dependent on renal function, with 78% of the dose recovered unchanged in the urine within the first 24 h.[22] In a pharmacokinetic study, the AUC increased in patients with impaired renal function; thus, pemetrexed was contraindicated in patients with a creatinine clearance < 45 mL/min.[26] In contrast, the AUC was approximately 20% lower in patients with a GFR ≥ 80 mL/min/1.73 m^2 than in those with a GFR 60–79 mL/min/1.73 m^2. Therefore, renal function in these patients may affect their clinical outcomes. However, the association of high renal function with chemotherapy efficacy and toxicity remains

unknown. Pemetrexed may be underdosed in patients with high GFR.

Thus, in this study, we aimed to investigate the effect of renal function on the efficacy and toxicity of CbP chemotherapy in patients with NS-NSCLC.

METHODS

Study design and patients

This was a post-hoc analysis of data from the PREDICT1 trial (CJLSG1201), a multicenter prospective observational study of CbP treatment followed by maintenance pemetrexed as front-line treatment (University Medical Information Network in Japan number, UMIN000008476).[27] This study protocol was approved by the institutional ethics committee of each participating institution, and written informed consent was obtained from all patients. The major inclusion criteria were as follows: age ≥ 20 years; histologically or cytologically diagnosed stage III disease not eligible for radical treatment including surgery or radiation; stage IV or recurrent NS-NSCLC; no history of prior chemotherapy; presence of at least one measurable lesion on computed tomography or magnetic resonance imaging following the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 criteria[28]; and adequate organ function, as deemed acceptable by the treating physician based on the information on the package insert of each agent. The exclusion criteria included a history of chest radiotherapy or other primary cancers. In the PREDICT1 study,[27] 500 mg/m^2 pemetrexed was administered, and since carboplatin clearance depends on the GFR, the carboplatin dose was determined using Calvert's formula as follows:

Carboplatin dose (mg) = target AUC × [GFR (mL/min) + 25].

The target AUC (5–6) was determined at the investigator's discretion. The cycles of combination therapy and administration of maintenance therapy with pemetrexed, as well as dose reduction, were determined by the investigator. The Ethics Review Committee of Nagoya University Graduate School of Medicine approved this study (No. 2018-0386). An opt-out method was used to obtain patients' consent, whereby participants could opt-out from being included, as per the tenets of the World Medical Association Declaration of Helsinki.

Treatment assessments

Tumors were assessed using computed tomography every 6 weeks for 36 weeks and then every 9 weeks thereafter. All responses were evaluated using the RECIST criteria. If a complete or partial response was observed, a confirmatory scan to assess the response was performed after at least 4 weeks. Patients who met stable disease criteria must have met the criteria at least once after the initiation of the study treatment at a minimum interval of 6 weeks. Progression-free survival (PFS) was measured as the interval from the start of the chemotherapy until either disease progression or any-cause death, whichever occurred first. Overall survival (OS) was measured as the time from the initiation of chemotherapy to any-cause death. Adverse events were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Renal toxicity was defined as grade 1 or higher creatinine level elevation.

Estimation of GFR

Because the actual GFR was not measured in the original observational study, the estimated GFR (eGFR)[29] was determined as follows:

eGFR (mL/min/1.73 m^2) = 194 × SCr$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female).

The patients were then divided into two groups based on baseline eGFR values: the high-eGFR group (eGFR ≥ 80 mL/min/1.73 m^2) and the low-eGFR group (eGFR < 80 mL/min/1.73 m^2).

Statistical analysis

The Mann–Whitney U test and the chi-squared test or Fisher exact test were used to evaluate continuous and binary variables, respectively. The Kaplan–Meier method was used to estimate survival, including PFS and OS. Multivariate Cox proportional hazards models were used to calculate hazard ratios of PFS and OS between groups. The models were adjusted for age (< 75 years or ≥ 75 years), sex (male or female), Eastern Cooperative Oncology Group performance status (0 or 1/2), smoking history (never or current/former), clinical stage (III/IV or recurrence), epidermal growth factor receptor mutation/anaplastic lymphoma kinase gene rearrangements (negative/unknown or positive), and initial carboplatin AUC (< 6 or 6). In exploratory analysis, we conducted a log-rank test for patients who received maintenance pemetrexed therapy. All statistical analyses were performed using JMP Pro version 17 (SAS Institute, Cary, NC, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Two-sided *P*-values < 0.05 were considered statistically significant.

RESULTS

Patient characteristics

Between July 2012 and June 2017, a total of 350 patients with advanced or recurrent previously untreated NS-NSCLC were included from 27 institutions in Japan (Figure 1). Among them, 12 patients were excluded because they were untreated (N = 7), they did not meet the inclusion criteria (N = 3), the regimen was changed before objective assessment of tumor responses (N = 1), or because of dual registration (N = 1). Finally, the GFR were estimated using the Japanese eGFR formula in 338 patients receiving CbP as first-line treatment. In total, 162 and 176 patients were categorized in the high-eGFR and the low-eGFR groups, respectively (Figure 1). Table 1 shows the baseline patient characteristics. The high-eGFR group was significantly younger than the low-eGFR group (median age, 66 years vs 72 years; $P < 0.0001$). The high-eGFR group also included a significantly lower proportion of patients aged ≥ 75 years (20 [12.3%] vs 49 [27.8%], $P = 0.0004$). Further, the postoperative recurrence rate was significantly lower in the high-eGFR group than in the low-eGFR group (5 [3.1%] vs 17 [9.7%], $P = 0.0057$). Meanwhile, sex and body surface area were similar in both groups. In addition, carboplatin with a target AUC of 6 was given to similar proportions of patients in each group.

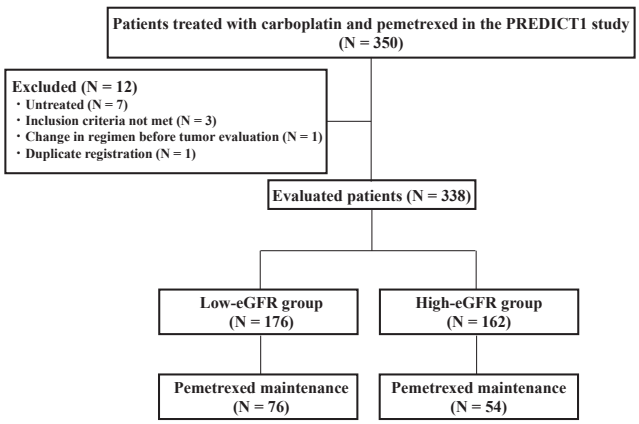

Fig. 1 Flowchart of the study design and patient selection
eGFR: estimated glomerular filtration rate

Table 1 Patient characteristics

Characteristic, N (%)		Total (N = 338)	Low-eGFR group[a] (N = 176)	High-eGFR group[b] (N = 162)	*P*-value
Age (years)	Median (range)	70 (40–82)	72 (44–82)	66 (40–79)	< 0.0001
	≥ 75	69 (20.4)	49 (27.8)	20 (12.3)	0.0004
Sex	Male	271 (80.2)	146 (83.0)	125 (77.2)	0.2191
	Female	67 (19.8)	30 (17.0)	37 (22.8)	
Smoking history	Current or former-smoker	282 (83.4)	145 (82.4)	137 (84.6)	0.6611
	Never smoker	56 (16.6)	31 (17.6)	25 (15.4)	
ECOG PS	0	154 (45.6)	84 (47.7)	70 (43.2)	0.1554
	1	160 (47.3)	84 (47.7)	76 (46.9)	
	2	24 (7.1)	8 (4.5)	16 (9.9)	
BSA (m^2)	Median (range)	1.62 (1.21–2.16)	1.63 (1.21–2.16)	1.60 (1.24–2.02)	0.1131
Histology	Adenocarcinoma	319 (94.4)	169 (96)	150 (92.6)	0.3136
	Large cell carcinoma	4 (1.2)	2 (1.1)	2 (1.2)	
	Others	15 (4.4)	5 (2.8)	10 (6.2)	
Stage	III	45 (13.3)	29 (16.5)	16 (9.9)	0.0057
	IV	271 (80.2)	130 (73.9)	141 (87)	
	Postoperative recurrence	22 (6.5)	17 (9.7)	5 (3.1)	
EGFR mutation or *ALK* fusion gene	Positive	41 (12.1)	24 (13.6)	17 (10.5)	0.4081
	Negative or unknown	297 (87.9)	152 (86.4)	145 (89.5)	
Serum creatinine (mg/dL)	Median (range)	0.73 (0.34–1.38)	0.84 (0.56–1.38)	0.62 (0.34–0.79)	< 0.0001
eGFR (mL/min/1.73 m^2)	Median (range)	78.5 (39.7–167.4)	67.4 (39.7–79.9)	93.7 (80–167.4)	< 0.0001
CrCl (mL/min)	Median (range)	74.5 (36.0–177.1)	62.8 (36.0–133.6)	92.1 (58.4–177.1)	< 0.0001
Target AUC of carboplatin	6	163 (48.2)	87 (49.4)	76 (46.9)	0.7015
	5.4	1 (0.3)	1 (0.6)	0	
	5	174 (51.5)	88 (50)	86 (53.1)	

ALK: anaplastic lymphoma kinase
AUC: area under the blood concentration-time curve
BSA: body surface area
CrCl: creatinine clearance
ECOG PS: Eastern Cooperative Oncology Group performance status
EGFR: epidermal growth factor receptor
eGFR: estimated glomerular filtration rate
[a] Patients with an eGFR < 80 mL/min/1.73 m^2
[b] Patients with an eGFR ≥ 80 mL/min/1.73 m^2

doi:10.18999/nagjms.87.3.483

Efficacy

The response rates were not significantly different between the high and low-eGFR groups (22.2% vs 23.9%, $P = 0.7205$; Table 2). However, the disease control rates were significantly lower in the high-eGFR group than in the low-eGFR group (75.9% vs 84.7%, $P = 0.043$). The median PFS was 4.0 months (95% CI, 3.6–4.5) in the high-eGFR group and 4.8 months (95% CI, 4.2–5.3) in the low-eGFR group. The adjusted hazard ratio for PFS was 1.32 (95% CI, 1.04–1.69; $P = 0.0245$; Figure 2A, Supplementary Table S1). The median OS was 10.0 months (95% CI, 8.6–12.4) in the high-eGFR group and 14.1 months (95% CI, 11.8–20.3) in the low-eGFR group. The adjusted hazard ratio for OS was 1.49 (95% CI, 1.15–1.93; $P = 0.0023$; Figure 2B, Supplementary Table S1).

Table 2 Objective tumor response

Variable, N (%)	Total (N = 338)	Low-eGFR group[a] (N = 176)	High-eGFR group[b] (N = 162)	*P*-value
Objective tumor response				
CR	3 (0.9)	3 (1.7)	0	
PR	75 (22.2)	39 (22.2)	36 (22.2)	
SD	194 (57.4)	107 (60.8)	87 (53.7)	
PD	58 (17.2)	21 (11.9)	37 (22.8)	
NE	8 (2.4)	6 (3.4)	2 (1.2)	
Response rate	78 (23.1)	42 (23.9)	36 (22.2)	0.7205
Disease control rate	272 (80.5)	149 (84.7)	123 (75.9)	0.043

CR: complete response
eGFR: estimated glomerular filtration rate
NE: not evaluable
PD: progressive disease
PR: partial response
SD: stable disease
[a] Patients with an eGFR < 80 mL/min/1.73 m^2
[b] Patients with an eGFR ≥ 80 mL/min/1.73 m^2

Among the patients who received maintenance pemetrexed, 54 and 76 patients belonged to the high and low-eGFR groups, respectively ($P = 0.0735$; Figure 1, Supplementary Table S2). As with the overall population, the proportion of patients aged ≥ 75 years was significantly lower in the high-eGFR group than in the low-eGFR group (6 [11.1%] vs 23 [30.3%], $P = 0.0106$). In addition, the proportion of patients with epidermal growth factor receptor or anaplastic lymphoma kinase mutations was significantly lower in the high-eGFR group than in the low-eGFR group (3 [5.6%] vs 16 [21.1%], $P = 0.0214$). The median PFS after maintenance treatment was 2.7 months (95% CI, 1.4–3.2) in the high-eGFR group and 3.4 months (95% CI, 2.3–4.9) in the low-eGFR group (Supplementary Figure S1A). The median OS was 13.9 months (95% CI, 10.2–17.1) in the high-eGFR group and 26.0 months (95% CI, 19.5–32.8) in the low-eGFR group (Supplementary Figure S1B). Both PFS and OS were significantly shorter in the high-eGFR group than in the low-eGFR group ($P = 0.012$ and $P = 0.0028$, respectively).

Subsequent therapy was administered to 111 of 162 patients (68.5%) in the high-eGFR group

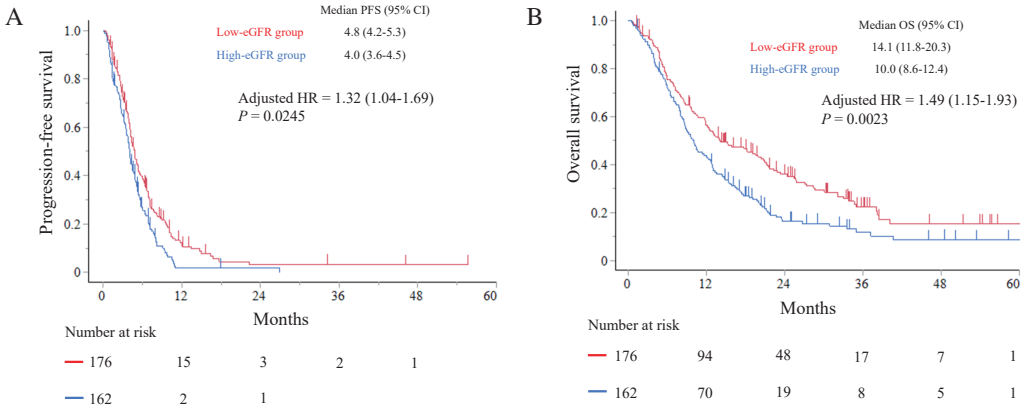

Fig. 2 Kaplan–Meier plots of survival

Fig. 2A: Progression-free survival
Fig. 2B: Overall survival
eGFR: estimated glomerular filtration rate
HR: hazard ratio
OS: overall survival
PFS: progression-free survival

and 106 of 176 patients (60.2%) in the low-eGFR group (P = 0.1397). Immune checkpoint inhibitors targeting programmed cell death-1/programmed cell death ligand-1 were administered to 33 patients (29.7%) in the high-eGFR group and to 31 patients (29.2%) in the low-eGFR group (P = 1.000). Inhibitors targeting epidermal growth factor receptor or anaplastic lymphoma kinase were used for 26 patients (23.4%) in the high-eGFR group and 25 patients (23.6%) in the low-eGFR group (P = 1.000).

Treatment exposure

The median number of cycles administered as combination therapy and maintenance therapy with pemetrexed was 4 and 3, respectively, in both groups. Among patients treated with maintenance therapy, more than six cycles of treatment were administered to 8 patients (14.8%) in the high-eGFR group and 22 patients (28.9%) in the low-eGFR group (P = 0.09). Dose reduction of carboplatin and/or pemetrexed occurred less frequently in the high-eGFR group than in the low-eGFR group (23 [14.2%] vs 41 [23.3%], P = 0.0373).

Safety

Regarding hematological toxicities, they were generally less common in the high-eGFR group than in the low-eGFR group (Table 3). Grade 3 or 4 neutropenia was observed less frequently in the high-eGFR group than in the low-eGFR group (47 [29%] vs 69 [39.2%], P = 0.0486). Similarly, the incidence of thrombocytopenia was significantly lower in the high-eGFR group than in the low-eGFR group (117 [72.2%] vs 149 [84.7%], P = 0.0076). Regarding non-hematological toxicities, renal toxicity and constipation also occurred less frequently in the high-eGFR group than in the low-eGFR group (renal toxicity, 35 [21.6%] vs 66 [37.5%], P = 0.0019; constipation, 103 [63.6%] vs 133 [75.6%], P = 0.018).

Table 3 Comparison of treatment-related adverse events between the low and high eGFR groups

	Low-eGFR group[a] (N = 176)		High-eGFR group[b] (N = 162)		*P*-value	
N (%)	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Hematological toxicity						
Neutropenia	131 (74.4)	69 (39.2)	106 (65.4)	47 (29)	0.071	0.0486
Anemia	166 (94.3)	46 (26.1)	152 (93.8)	48 (29.6)	1	0.5437
Thrombocytopenia	149 (84.7)	60 (34.1)	117 (72.2)	51 (31.5)	0.0076	0.6439
Non-hematological toxicity						
Febrile neutropenia	14 (8.0)	14 (8.0)	5 (3.1)	5 (3.1)	0.0605	0.0605
AST increased	98 (55.7)	2(1.1)	82 (50.6)	4 (2.5)	0.3833	0.432
ALT increased	98 (55.7)	4 (2.3)	87 (53.7)	7 (4.3)	0.7435	0.3641
Bilirubin increased	28 (15.9)	0	20 (12.3)	1 (0.6)	0.4358	0.4793
Renal toxicity	66 (37.5)	0	35 (21.6)	0	0.0019	–
Nausea	115 (65.3)	6 (3.4)	104 (64.2)	8 (4.9)	0.9093	0.5884
Vomiting	37 (21)	2 (1.1)	39 (24.1)	2 (1.2)	0.517	1
Diarrhea	22 (12.5)	2 (1.1)	29 (17.9)	2 (1.2)	0.1744	1
Constipation	133 (75.6)	10 (5.7)	103 (63.6)	11 (6.8)	0.018	0.8222
Fatigue	124 (70.5)	19 (10.8)	125 (77.2)	21 (13.0)	0.1753	0.6141
Appetite loss	136 (77.3)	18 (10.23)	129 (79.6)	21 (13.0)	0.6916	0.4967

AST: aspartate aminotransferase
ALT: alanine aminotransferase
eGFR: estimated glomerular filtration rate
[a] Patients with an eGFR < 80 mL/min/1.73 m^2
[b] Patients with an eGFR ≥ 80 mL/min/1.73 m^2

DISCUSSION

In the current post-hoc analysis using data obtained from a multicenter prospective observational study of CbP treatment in patients with NS-NSCLC, the patients were divided into two groups according to their eGFR. Although the response rate was similar between the high- and low-eGFR groups, the disease control rate was significantly lower in the high-eGFR group than in the low-eGFR group. PFS and OS were also significantly shorter in the high-eGFR group than in the low-eGFR group. Regarding adverse events, the incidence of hematological and non-hematological toxicities were significantly lower in the high-eGFR group. Collectively, these results indicate that renal function, as calculated using the Japanese equation, is associated with the clinical efficacy and toxicity of CbP in patients with NS-NSCLC.

Pemetrexed is eliminated by renal excretion; therefore, the AUC of this agent may be influenced by renal function.[22] In a pharmacokinetic study,[26] patients with a GFR of 30–39 mL/min/1.73 m^2 showed two times higher AUC than did those with a GFR of 60–79 mL/min/1.73 m^2. Previous retrospective studies have reported a higher incidence of pemetrexed-induced toxicity in patients with impaired renal function.[30-32] In addition, patients with NS-NSCLC treated with continuation maintenance therapy with pemetrexed and a creatinine clearance < 60mL/min had significantly longer survival.[32] In contrast, high renal function may be associated with a decreased AUC of pemetrexed. The AUC[26] was approximately 20% lower in patients with a GFR ≥ 80 mL/min/1.73 m^2 than in those with a GFR 60–79 mL/min/1.73 m^2. In the current study, patients with high-eGFR showed lower disease control rate and shorter PFS and OS than did those with

low-eGFR, even after adjustment for patient characteristics including presence of epidermal growth factor receptor mutations/anaplastic lymphoma kinase gene mutations. In line with a previous study,[32] patients with a low-eGFR treated with maintenance pemetrexed had significantly longer PFS and OS than those with a high-eGFR. Some hematological and non-hematological toxicities were also significantly less common in the high-eGFR group than in the low-eGFR group, indicating potential underdosing in patients with a high-eGFR. In an early phase I study,[22] the maximally tolerated dose was 600 mg/m^2; however, in subsequent phase II studies, a reduced starting dose of 500 mg/m^2 was recommended owing to toxicities.[23,33] Pemetrexed treatment is better tolerated with folic acid and vitamin B_{12} supplementation than without supplementation.[25] Additionally, pemetrexed at a dose of 1,050 mg/m^2 was tolerated under high-dose folic acid or multivitamin supplementation.[34] In addition, two randomized control studies comparing standard- and high-dose pemetrexed as second-line treatment in patients with NSCLC demonstrated similar efficacy but slightly higher toxicities with high-dose pemetrexed than with standard-dose pemetrexed. Although these two trials did not assess the patients' renal function, they indicated the potential to increase the dose of pemetrexed, especially in patients with a high-eGFR.[35,36] A recent study[37] exploring optimized dosing based on renal function failed to show superiority compared to standard dosing, potentially because the enrolled patients had a high-eGFR, with median value of 90.1 mL/min/1.73 m^2 (range, 80.9–98.9 mL/min/1.73 m^2). Taken together, these results suggest that eGFR evaluation may be important for treatment with CbP in patients with NS-NSCLC, not only in terms of toxicities but also in terms of efficacy, and that the dose of pemetrexed could potentially be increased, especially for patients with a high-eGFR.

In general, patients with chronic kidney disease and cancer have a poorer prognosis than the general population.[38,39] However, the association between renal function and prognosis in patients with NSCLC remains unclear. A previous study[40] reported poorer prognosis in lung cancer patients with an eGFR < 60 mL/min/1.73 m^2 than in those with an eGFR ≥ 60 mL/min/1.73 m^2. In contrast, another study reported that a higher baseline creatinine clearance level was significantly associated with worse OS in patients with NSCLC who received chemotherapy.[41] Data on specific chemotherapeutic agents were not shown, and statistical significance was observed only in univariate analyses; however, our results may be in line with these findings.

The following limitations of this study should be noted. First, this study was a post-hoc analysis; therefore, an imbalance in patient characteristics between the groups could exist. As shown in Table 1, some factors were significantly different between the high- and low-eGFR groups. However, the patient characteristics and these factors were adjusted for in the multivariate analyses, and the results revealed that high-eGFR was independently associated with poor PFS and OS. Second, the patients received both carboplatin and pemetrexed; therefore, carboplatin may have affected the clinical course. In addition, the initial dose or dose reduction of carboplatin was determined at the investigator's discretion. However, the target AUC was also adjusted in the multivariate analysis, indicating minimization of the effect of carboplatin. Moreover, the carboplatin dose is determined using Calvert's formula based on GFR, which is substituted with creatinine clearance calculated using the Cockcroft-Gault formula in daily practice. This indicates that renal function is considered in the dose calculation. Third, we used the eGFR instead of the actual GFR, which was not measured because the study was a post-hoc analysis. The eGFR is widely used in the clinical assessment of chronic kidney disease. Inulin clearance is the most widely accepted measure for evaluating actual GFR. However, its measurement is complicated, and thus, it is not commonly performed in clinical practice, with eGFR often being used instead. In addition, the actual AUCs of pemetrexed and carboplatin were not measured. Our results need to be validated in a randomized controlled trial, and further studies regarding the dose adjustment of pemetrexed based on renal function are warranted.

In conclusion, renal function influences the efficacy and toxicity of CbP chemotherapy in patients with NS-NSCLC. Thus, eGFR evaluation may be informative for predicting treatment responses in these patients.

CONFLICT OF INTEREST

T Hase received personal fees from AstraZeneca KK, Takeda Pharmaceutical Co Ltd, Chugai Pharmaceutical Co Ltd, Ono Pharmaceutical Co Ltd, Bristol-Myers Squibb Co Ltd, Taiho Pharmaceutical Co Ltd, MSD KK, Merck Biopharma Co Ltd, Pfizer Inc, and Eli Lilly Japan KK and grants from Novartis Pharma KK, AstraZeneca KK, BeiGene Inc, AbbVie Inc, Amgen Co Ltd, and Chugai Pharmaceutical Co Ltd, outside of the submitted work. TK received personal fees from AstraZeneca KK. MI reports lecture fees from AstraZeneca, GlaxoSmithKline, Insmed, Boehringer Ingelheim and research funding from Nippon Boehringer Ingelheim Co, Ltd. All other authors have no conflicts of interest to declare.

ACKNOWLEDGMENTS

We would like to thank all those who participated in the study. This post-hoc analysis used data collected from PREDICT1/CJLSG1201, which was a collaborative effort of the Central Japan Lung Study Group and the Chubu Regional Consortium for Advanced Medicine. We would also like to thank Editage (www.editage.com) for English language editing.

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Nagoya J. Med. Sci. 87. 483–497, 2025

doi:10.18999/nagjms.87.3.483

SUPPLEMENTARY INFORMATION

Suppl Table S1 Univariate and multivariate analysis for PFS and OS

		PFS				OS			
		Univariate		Multivariate		Univariate		Multivariate	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)	< 75	1.21 (0.91-1.61)	0.1789	1.11 (0.83–1.49)	0.4662	1.12 (0.82–1.52)	0.4675	1.03 (0.75–1.41)	0.8571
	≥ 75	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Sex	Female	0.86 (0.65–1.15)	0.3075	1.12 (0.74–1.70)	0.5945	0.50 (0.36–0.70)	<0.0001	0.59 (0.37–0.93)	0.0228
	Male	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
ECOG-PS	0	0.89 (0.71–1.12)	0.3098	0.92 (0.73–1.17)	0.4981	0.70 (0.55–0.90)	0.0051	0.68 (0.53–0.88)	0.0029
	1 or 2	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Smoking history	Never	0.68 (0.50–0.93)	0.0171	0.67 (0.42–1.08)	0.0985	0.45 (0.31–0.66)	<0.0001	0.78 (0.46–1.32)	0.3528
	Ever	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Stage	Recurrence	0.76 (0.48–1.20)	0.234	0.78 (0.48–1.25)	0.3035	0.74 (0.44–1.25)	0.2676	0.74 (0.43–1.27)	0.2768
	III or IV	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Somatic mutations (*EGFR* or *ALK*)	Positive	0.66 (0.46–0.95)	0.0247	0.76 (0.52–1.11)	0.1551	0.46 (0.31–0.68)	0.0001	0.55 (0.36–0.84)	0.0051
	Unknown or negative	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Carboplatin AUC	6	0.88 (0.70–1.11)	0.2786	0.85 (0.67–1.08)	0.1858	0.82 (0.65–1.05)	0.1226	0.75 (0.58–0.96)	0.0224
	< 6	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
eGFR	≥ 80 mL/min/1.73 m^2	1.44 (1.14–1.81)	0.0022	1.32 (1.04–1.69)	0.0245	1.50 (1.17–1.91)	0.0013	1.49 (1.15–1.93)	0.0023
	< 80 mL/min/1.73 m^2	1 (ref)		1 (ref)		1 (ref)		1 (ref)	

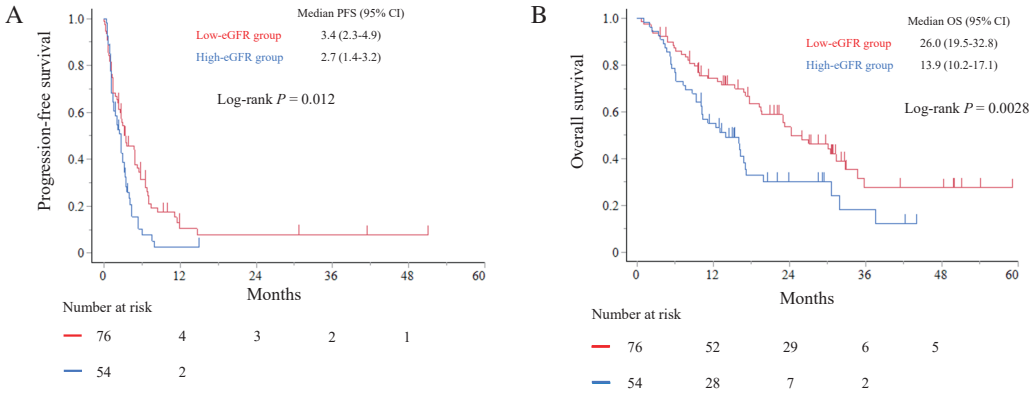
ALK: anaplastic lymphoma kinase
AUC: area under the blood concentration-time curve
ECOG PS: Eastern Cooperative Oncology Group performance status
EGFR: epidermal growth factor receptor
eGFR: estimated glomerular filtration rate
HR: hazard ratio
OS: overall survival
PFS: progression-free survival

Suppl Table S2 Characteristics of the patients who received maintenance pemetrexed

Characteristic, N (%)		Total (N = 130)	Low-eGFR group[a] (N = 76)	High-eGFR group[b] (N = 54)	*P*-value
Age (years)	Median (range)	70 (40–82)	72 (44–82)	66 (40–79)	0.0004
	≥ 75	29 (22.3)	23 (30.3)	6 (11.1)	0.0106
Sex	Male	101 (77.7)	59 (77.6)	42 (77.8)	1
	Female	29 (22.3)	17 (22.4)	12 (22.2)	
Smoking history	Current or former-smoker	103 (79.2)	57 (75)	46 (85.2)	0.1914
	Never smoker	27 (20.8)	19 (25)	8 (14.8)	
ECOG PS	0	67 (51.5)	38 (50)	29 (53.7)	0.3599
	1	59 (45.4)	37 (48.7)	22 (40.7)	
	2	4 (3.1)	1 (1.3)	3 (5.6)	
BSA (m^2)	Median (range)	1.62 (1.21–2.16)	1.63 (1.21–2.16)	1.57 (1.27–1.99)	0.1195
Histology	Adenocarcinoma	127 (97.7)	74 (97.4)	53 (98.1)	1
	Large cell carcinoma	1 (0.8)	1 (1.3)	0	
	Others	2 (1.5)	1 (1.3)	1 (1.9)	
Stage	III	17 (13.1)	11 (14.5)	6 (11.1)	0.1483
	IV	101 (77.7)	55 (72.4)	46 (85.2)	
	Postoperative recurrence	12 (9.2)	10 (13.2)	2 (3.7)	
EGFR mutation or *ALK* fusion gene	Positive	19 (14.6)	16 (21.1)	3 (5.6)	0.0214
	Negative or unknown	111 (85.4)	60 (78.9)	51 (94.4)	
Serum creatinine (mg/dL)	Median (range)	0.73 (0.38–1.38)	0.83 (0.56–1.38)	0.625 (0.38–0.75)	< 0.0001
eGFR (mL/min/1.73 m^2)	Median (range)	76.0 (39.7–131.9)	66.9 (39.7–79.6)	93.1 (80.0–131.9)	< 0.0001
CrCl (mL/min)	Median (range)	74.0 (40.1–170.8)	65.6 (40.1–133.6)	89.8 (58.4–170.8)	< 0.0001
Target AUC of carboplatin	6	68 (52.3)	38 (50)	30 (55.6)	0.5947
	5	62 (47.7)	38 (50)	24 (44.4)	

ALK: anaplastic lymphoma kinase
AUC: area under the blood concentration-time curve
BSA: body surface area
CrCl: creatinine clearance
ECOG PS: Eastern Cooperative Oncology Group performance status
EGFR: epidermal growth factor receptor
eGFR: estimated glomerular filtration rate
[a] Patients with an eGFR < 80 mL/min/1.73 m^2
[b] Patients with an eGFR ≥ 80 mL/min/1.73 m^2

doi:10.18999/nagjms.87.3.483



Suppl Fig. S1 Kaplan–Meier plots of survival after receiving maintenance pemetrexed
Suppl Fig. S1A: Progression-free survival
Suppl Fig. S1B: Overall survival
eGFR: estimated glomerular filtration rate
HR: hazard ratio
OS: overall survival
PFS: progression-free survival