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Original Article

Retrospective Cohort Study of Clinical Efficacy and Safety of Cefozopran for Treating Febrile Neutropenia during Chemotherapy in Patients with Lung Cancer

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Febrile neutropenia (FN) is a serious side effect in patients undergoing cancer chemotherapy and frequently proves fatal. Since infection control is crucial in the management of FN, the antimicrobial agent cefozopran (CZOP) has been recommended but not approved for routine use in clinical care of FN in Japan. However, few studies of CZOP in the management of FN have used a thrice daily dose schedule. The aim of this study was to retrospectively compare the efficacy and safety of CZOP at a dose of 1 g three times daily to those of cefepime (CFPM) in the treatment of FN in our lung cancer patients. The response rates of the CZOP and CFPM groups were 89.5% (17/19 cases) and 83.0% (39/47 cases), respectively, with no significant difference between the two groups. The median duration of antimicrobial treatment was 6 days (4-10 days) in the CZOP group and 7 days (3-13 days) in the CFPM group, with no significant difference between groups. The incidence rates of adverse events were 21.1% (4/19 cases) in the CZOP group and 19.1% (9/47 cases) in the CFPM group. No adverse events of Grade 3 or higher were observed in either group. The findings of the present study suggest that CZOP administration at a dose of 1 g three times per day as an antimicrobial treatment alternative against FN.

Key words: febrile neutropenia, cefozopran, cefepime, lung cancer, retrospective

Febrile neutropenia (FN) is a serious complication in patients undergoing cancer chemotherapy and proves to be fatal in many patients. In particular, FN caused by gram-negative bacilli such as *Pseudomonas aeruginosa* has a case fatality rate as high as 40% and is often not appropriately treated with antimicrobials [1,2].

Although four antimicrobials, cefepime (CFPM), tazobactam/piperacillin (TAZ/PIPC), meropenem (MEPM), and vancomycin (VCM), have been approved for the treatment of FN in Japan, only TAZ/PIPC or CFPM are advised as first-line drugs for this condition. High-dose and long-term administration of VCM for the treatment of patients with FN frequently results in renal dysfunction and other complications; therefore, VCM administration should be restricted for patients that are likely to have methicillin-resistant *Staphylococcus aureus* infection [3,4]. In addition, MEPM and other carbapenem antimicrobials should be used only against infection with antimicrobial-resistant bacteria that produce enzymes, such as extended-spectrum beta-lactamase or AmpC beta-lactamase (AmpC) [5-7]. Hence, TAZ/PIPC or CFPM, antipseudomonal beta-lactam antimicrobials, are used as monotherapy for first-line treatment of FN, with reference to anti-

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biograms of clinical bacterial isolates in each institution. However, there is little evidence for alternative antimicrobial agents that could be used when these agents are unavailable (for example, during interrupted supplies). Disasters such as earthquakes and contamination of active pharmaceutical ingredients cause frequent interruptions in the supply of antimicrobial agents in Japan.

Cefozopran (CZOP) is an extended-spectrum fourth-generation cephem antimicrobial developed in Japan. CZOP is listed in the Japanese clinical guidelines for FN treatment as a routine drug for clinical care, though it has not been approved for FN in Japan. CZOP is well-known as a broad-spectrum agent, and many comparative studies have demonstrated its efficacy as an empirical monotherapy for FN [8, 9]. In all the FN studies, however, CZOP has been administered twice daily. Pharmacokinetics-pharmacodynamics optimization demands frequent administration of beta-lactams to increase the proportion of time serum levels are above the minimum inhibitory concentration [10]. Therefore, we speculated that efficacy of CZOP would improve if it were administrated at a dose of 1 g three times per day, as we routinely used it in our hospitalized FN patients. The present study aimed to retrospectively assess the efficacy and safety of CZOP administered at a dose of 1 g three times per day in patients with lung cancer and FN, and to compare the results with those of CFPM, which is approved for FN treatment, at a dose of 2 g twice a day.

Materials and Methods

Patients. This study was conducted as a retrospective cohort study. Among patients with lung cancer hospitalized at the Allergy and Respiratory Medicine Unit of the Okayama University Hospital from August 2016 to March 2020, those who developed FN during chemotherapy with cytotoxic anti-cancer drugs and who were administered either CZOP or CFPM were selected for the study. Patients administered CZOP at a dose of 1 g three times per day were assigned to the CZOP group, and patients administered CFPM at a dose of 2 g twice per day were assigned to the CFPM group. Patients treated with CZOP were separated from the CFPM group and those treated with CFPM were separated from the CZOP group. Regarding CFPM, the supply of the generic drug was stopped in 2014; the supply of brand-name versions also became insufficient from around June 2018, making it difficult to routinely use CFPM in cancer patients at the onset of FN. Moreover, CZOP is listed in the guidelines for FN treatment as a drug used routinely in clinical care. The package insert states, "for refractory or severe infections, increase the dose to 4 g daily and administer in 2-4 divided doses". Therefore, CZOP was used as an alternative for treating lung cancer patients at the onset of FN. FN is defined as a condition with axillary temperature ≥ 37.5°C and a neutrophil count ≤ 500/μL, or a neutrophil count ≤ 1,000/μL that is likely to decrease ≤ 500/μL within 48 h.

Retrospective chart review study was conducted that included the following patient background data: sex, age, histological type, Eastern Cooperative Oncology Group performance status (ECOG-PS), smoking status, treatment line, regimen, serum creatine concentration, estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), neutrophil count, days of neutrophil count ≤ 1,000/μL, Multinational Association of Supportive Care in Cancer (MASCC) score, antimicrobial dosing days, use of granulocyte-colony stimulating factor (G-CSF) drugs, use of antipyretic drugs, detection of microorganisms in blood cultures prior to the administration of antimicrobial therapy, and adverse events after antimicrobial administration.

Patients with hepatic dysfunction (AST/ALT > 100 U/L), renal dysfunction (eGFR < 50 mL/min/1.73 m^2), allergic history of CZOP or CFPM administration, or adverse events during administration of CZOP or CFPM were excluded.

Response criteria. The response rate was the primary endpoint of this study. Assessment of the efficacy of antimicrobial treatment was based on the approaches used in previous studies [9]. The study cases were divided into four groups: excellent improvement, moderate improvement, mild improvement, and no response. Excellent improvement was defined by a decrease in axillary temperature below 37°C within 3 days of the initial drug administration, retention of temperature below 37°C for more than 3 days, and improvement of clinical condition and examination findings related to infection. Moderate improvement was defined as a decrease in axillary temperature to below 37°C within 7 days of the initial drug administration, with clinical condition and examination findings related to infection also showing improvement.

Mild improvement was defined as a trend of decline in axillary temperature within 7 days of the initial drug administration, together with improvement in clinical condition and examination findings related to infection. Contrarily, cases that showed no trend of decline in axillary temperature at 7 days after initiation of drug therapy, and clinical condition and examination findings related to infection remained unchanged or exacerbated, or in which the drug was changed owing to lack of any sign of decline of the fever were described as "no response". In addition, the response rate of the antimicrobials was defined as the sum of the rates of excellent, moderate, and mild improvement.

Adverse events. The severity of clinical conditions and laboratory data were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

Statistical analysis. To evaluate the efficacy and safety of antimicrobials, Fisher's exact test was conducted between the two groups. Fisher's exact test was conducted to assess differences based on sex, histological type, ECOG-PS, smoking status, treatment line, and use of anticancer, antipyretic, and G-CSF drugs between the two groups. Student's *t*-test was conducted to assess differences based on age, pack-years, MASCC score, serum creatinine, eGFR, CRP, neutrophil count, days of neutrophil count ≤1,000/μL, and days the initial antibiotic was administered between the two groups. Statistical significance was set at $p < 0.05$.

Ethical considerations. This study was approved by the Ethics Committee of the Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama University (Ken 2001-08). All the activities of this study were performed in compliance with the "Ethics Guidelines for Medical Research performed on Human Subjects."

Results

Study patients. Clinical characteristics of the patients are presented in Table 1. The study involved a total of 66 patients, including 19 patients in the CZOP group (15 men and 4 women) and 47 patients in the CFPM group (28 men and 19 women). There were no statistically significant differences between the two groups with respect to clinical characteristics of the patients, including age at the onset of FN, PS, treatment line, serum creatinine concentration, eGFR, CRP, neutrophil count, and MASCC score. There were significant differences in the use of immune checkpoint inhibitors (ICIs) between the CZOP group (47.4%, 9/19) and CFPM group (10.6%, 4/47).

Regarding the use of G-CSF drugs, 47.4% and 51.1% of the total patients in the CZOP group (9/19) and CFPM group (24/47), respectively, were administered these drugs, with no significant difference between the two groups. Moreover, 52.6% (10/19) and 68.1% (32/47) of patients in the CZOP group and CFPM group, respectively, were administered antipyretic drugs.

Pre-antimicrobial blood culture was observed to be positive for *Klebsiella pneumoniae* in one case of the CFPM group. On the contrary, no pathogen was isolated from cultured blood in the CZOP group. Further, no significant difference between the two groups was observed regarding the days of neutrophil count ≤1,000/μL (minimum value–maximum value), which were estimated as 6 (3-9) in the CZOP group and 7 (3-13) in the CFPM group. Furthermore, no significant difference between the two groups was observed in the median dosing days, which were estimated as 6 (4-10) in the CZOP group and 7 (3-13) in the CFPM group.

Clinical efficacy. The clinical efficacy assessment showed that CZOP treatment resulted in seven cases with excellent improvement (36.8%), eight with moderate improvement (42.1%), two with mild improvement (10.5%), and two with no response (10.5%), while CFPM treatment resulted in 12 cases with excellent improvement (25.5%), 18 with moderate improvement (38.3%), nine with mild improvement (19.1%), and eight with no response (17.0%) (Table 2).

The response rates were 89.5% (17/19 cases) in the CZOP group and 83.0% (39/47cases) in the CFPM group, with no statistically significant difference between the two groups (ORR = 1.74, 95%CI; 0.34–9.09, $p = 0.71$).

Adverse events. Adverse event incidence rates were 21.1% (4/19 cases) in the CZOP group and 19.1% (9/47 cases) in the CFPM group (ORR = 1.13, 95%CI; 0.30-4.21, $p = 1.00$) (Table 3). Specifically, in the CZOP vs. CFPM groups, AST levels increased by 15.8% vs. 8.5%, ALT levels increased by 15.8% vs. 10.6%, skin rashes were observed in 10.5% vs. 2.1%, and diarrhea occurred in 0.0% vs. 8.5%, respectively. No adverse events of Grade 3 or higher were observed in either the CZOP or CFPM groups (Table 4).

Table 1 Clinical characteristics of the patients

	CZOP (n=19) median (range) or n (%)	CFPM (n=47) median (range) or n (%)	*P*-value
Sex male, n (%)	15 (78.9%)	28 (59.6%)	0.16
Age (year)	69 (42–75)	68 (42–78)	0.64
Histological type			
Adenosquamous carcinoma	11 (57.9%)	25 (53.2%)	0.78
Squamous cell carcinoma	1 (5.3%)	6 (12.8%)	
Small cell carcinoma	5 (26.3%)	13 (27.7%)	
Others	2 (10.5%)	3 (6.4%)	
ECOG-PS			
0–1	16 (84.2%)	43 (91.5%)	0.21
2	3 (15.8%)	2 (4.3%)	
3	0 (0.0%)	2 (4.3%)	
Smoking status			
Former/Current Smoker	15 (78.9%)	36 (76.6%)	1.00
Pack-years	43 (12–98)	34 (1–84)	0.26
non-smoker	4 (21.1%)	11 (23.4%)	
Treatment line			
1st	10 (52.6%)	27 (57.4%)	0.77
2nd	2 (10.5%)	3 (6.4%)	
3rd≤	7 (36.8%)	17 (36.2%)	
Regimen			
Use of Anticancer			
platinum doblet	14 (73.7%)	27 (57.4%)	0.27
others	5 (26.3%)	20 (42.6%)	
Use of ICI	9 (47.4%)	5 (10.6%)	0.002
MASCC score	21 (14–23)	21 (18–24)	0.10
Serum creatinine (mg/dL)	0.83 (0.51–1.10)	0.72 (0.37–1.16)	0.52
eGFR (mL/min/1.73 m^2)	70.9 (51.4–109.4)	68.9 (50.1–134.6)	0.47
CRP (mg/dL)	5.46 (0.80–19.35)	2.87 (0.17–31.93)	0.16
Neutrophil count at onset (/μL)	210 (0–991)	279 (3–990)	0.88
Days of neutrophil count ≤1,000/μL	6 (3–9)	7 (3–13)	0.42
Use of G-CSF	9 (47.4%)	24 (51.1%)	1.00
Use of antipyretics	10 (52.6%)	32 (68.1%)	0.27
Administered days of initial antibiotics (days)	6 (4–10)	7 (3–13)	0.61

Table 2 Clinical efficacy

	CZOP	CFPM	Odds ratio	95%CI	*p*-value
Response rate	17 (89.5%)	39 (83.0%)	1.74	0.34–9.09	0.81
Excellent improvement	7 (36.8%)	12 (25.5%)			
Moderate improvement	8 (42.1%)	18 (38.3%)			
Mild improvement	2 (10.5%)	9 (19.1%)			
No response	2 (10.5%)	8 (17.0%)			

Discussion

In our study, the response rates of CZOP and CFPM in patients with lung cancer and FN were 89.5% and 83.0%, respectively. The median duration of antimicrobial treatment was 6 days (4-10 days) in the CZOP group and 7 days (3-13 days) in the CFPM group, with no significant difference between the two groups. Despite administration of high-dose CFPM at 2 g twice per day, compared to CZOP at 1 g thrice per day, there was no difference in efficacy.

Similarly, Sarashina *et al.* reported no differences in

Table 3 Incidence rates of individual adverse events

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Incident rate
CZOP							
AST increase	3					3	15.8%
ALT increase	3					3	15.8%
Skin Rash	2					2	10.5%
Diarrhea						0	0.0%
CFPM							
AST increase	3	1				4	8.5%
ALT increase	5					5	10.6%
Skin Rash	1					1	2.1%
Diarrhea	4					4	8.5%

Grade 1-5 is based on Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Table 4 Overall incidence rates of adverse events

Adverse events	Incident rate	Odds ratio	95%CI	*p*-value
CZOP	21.1%	1.13	0.30–4.21	1.00
CFPM	19.1%			

the efficacy and safety between CZOP- and CFPM-administered groups [11]. Nakane *et al.* conducted an open-label, randomized study to evaluate the clinical efficacy of CZOP, CFPM, MEPM, and imipenem-cilastatin (IPM/CS) in patients with FN [12]. They reported that CZOP (2 g, q12 h) was inferior to CFPM (2 g, q12 h). However, both these previous studies implemented twice-daily administration for all antimicrobials, including CZOP. Based on the pharmacokinetics-pharmacodynamics optimization theory, CZOP may not have shown adequate antimicrobial activity in these previous studies because it was not administered frequently enough.

Moreover, according to the study by Nakane *et al.*, the incidence rates of side effects were 5.3% in the CZOP group (1 g twice per day) and 9.7% in the CFPM group (2 g twice per day), with no significant difference; the respective dropout rates were 2.1% and 4.3% [12]. The incidence rates of side effects in our study were higher: 21.1% in the CZOP group and 19.1% in the CFPM group. However, there was no difference in the incidence rates of side effects between the two groups, consistent with the previous reports.

In this study, the number of patients using ICIs was significantly higher in the CZOP group. It is thought that activation of the immune response, *e.g.* by ICIs, impacts the therapeutic effect of antimicrobials on infectious diseases. However, our study included patients with lung cancer who developed FN using cytotoxic chemotherapy and who did not have fever associated with infusion reaction or an immune reaction due to ICI administration. Furthermore, there was no significant difference between the groups in neutrophil count at onset and days of Grade 3 neutropenia. Thus, it was considered that the administration of ICIs did not influence the therapeutic efficacy of antibiotics.

The present study has limitations. First, the number of lung cancer patients was small. Second, the efficacy of CZOP for FN developed during treatment of other carcinomas was not evaluated. Therefore, further studies with a larger sample size and confounding adjustments are needed.

In conclusion, we demonstrated the comparative efficacy and safety of CZOP to CFPM, which is a first-line drug for FN, in this retrospective study. Considering the recent trends of FN-causing bacteria, CZOP may prove a better alternative, at least in lung-cancer patients. In Japan, the supply of CFPM has been restricted since 2014 because of the difficulty in procurement of the active pharmaceutical ingredient. When the supply of antibacterial drugs is insufficient, CZOP administration at a dose of 1 g three times per day can be considered as an effective and safe antimicrobial treatment alternative for FN in lung cancer patients.

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