Risk Factors for Febrile Neutropenia Induced by Docetaxel Chemotherapy in Patients with Non-small Cell Lung Cancer

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We retrospectively obtained data of patient background and pretreatment characteristics from medical records and identified the predictive factors of febrile neutropenia (FN) in patients with non-small cell lung cancer (NSCLC) treated with docetaxel alone or in combination with the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab. Patients were eligible for inclusion in the study if they were 20 years or older, diagnosed with NSCLC, and received docetaxel monotherapy alone or in combination with bevacizumab at the Department of Respiratory Medicine, Kobe City Medical Center General Hospital, between July 1, 2011, and March 31, 2018. Eighty-one patients with recurrent or advanced NSCLC were included. Multivariate stepwise logistic regression analysis with backward selection revealed that lower baseline Eastern Cooperative Oncology Group performance status (ECOG-PS) scores of 1 and 2 (odds ratio (OR), 5.098; 95% confidence interval (CI), 1.045–24.879, p = 0.021) and baseline platelet count below 18.8 µg/mL (OR, 3.861; 95% CI, 1.211–12.311, p = 0.022) were significant factors influencing the FN occurrence rate. Our results demonstrated that ECOG-PS 1–2 and lower baseline platelet count were significant risk factors of FN in patients with NSCLC receiving docetaxel-based chemotherapy. Moreover, the combination of anti-VEGF antibodies and docetaxel might be associated with increased FN frequency. Despite the limitations of this study including its retrospective design, single-center site, and small sample size, baseline ECOG-PS score and platelet count may be regarded as important indices to identify patients for prophylactic granulocyte-colony stimulating factor (G-CSF) treatment before docetaxel-based chemotherapy.

Key words docetaxel; febrile neutropenia; risk factor; performance status; platelet count

INTRODUCTION

Lung cancer is one of the most common types of cancer and the leading cause of cancer-related deaths worldwide, with more than 1.59 million deaths.1,2) Among Asian countries, Japan has experienced high incidence and mortality due to lung cancer,3) with mortality in males being approximately twice than that in females.3) Among the two major types of lung cancer, namely, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), approximately 85% of lung cancer patients are diagnosed with NSCLC.

Docetaxel, an anti-tubulin agent, is an effective cytotoxic drug for the treatment of NSCLC,4) and it is recommended for use as monotherapy or in combination with multi-targeted drugs for refractory or recurrent cases after platinum-based chemotherapy for NSCLC.5–8) The anti-vascular endothelial growth factor (VEGF) antibody bevacizumab can be used in first-line therapy in combination with docetaxel in elderly patients with advanced NSCLC.9,10) However, docetaxel is often associated with adverse effects including neutropenia, leukopenia, dermatitis, edema, and anaphylaxis, among which neutropenia is the most severe.11–13) Neutrophils are the most abundant type of white blood cell, accounting for 60–70% of the circulating leukocytes, and they help in providing primary defense against bacterial infections.14) Patients receiving docetaxel chemotherapy are susceptible to bacterial infections. Febrile neutropenia (FN), defined as the presence of fever and a low neutrophil count, is also a serious complication of docetaxel chemotherapy and often induces fatal infection. With the onset of FN, patients should be given prompt medical intervention.15) To prevent this condition, it is important to clarify the risk factors of severe neutropenia in patients receiving docetaxel chemotherapy.

To predict the probability of FN occurrence, Ozawa et al. developed an equation that incorporated performance status (PS) as a significant covariate in Japanese patients with NSCLC and other types of cancer receiving docetaxel therapy.15) Fukae et al. also performed a population pharmacokinetic–pharmacodynamic analysis in Japanese NSCLC patients treated with docetaxel-based chemotherapy, showing that levels of albumin and α1-acid glycoprotein in serum were closely related to the time course of neutrophil count and neutropenia development.16) However, serum α1-acid glycoprotein levels are not routinely monitored in daily practice, and its clinical usefulness is not clear as a predictive factor for neutropenia in NSCLC patients receiving docetaxel chemotherapy. In the present study, we retrospectively obtained data on patient background and pretreatment characteristics from medical records and identified the predictive factors of FN in NSCLC patients treated with docetaxel alone or in combination with bevacizumab.

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MATERIALS AND METHODS

Study Design, Setting, and Patient Population This study was conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan. The protocol was approved by the Ethics Committee of Kobe City Medical Center General Hospital (Approval No. zn 180625). The need for informed consent was waived for the retrospective design of the study. Patients were eligible for the study if they were 20 years or older, diagnosed with NSCLC, and received docetaxel monotherapy or in combination with multi-targeted drugs at the Department of Respiratory Medicine, Kobe City Medical Center General Hospital, between July 1, 2011, and March 31, 2018.

Treatment Schedule Chemotherapy included docetaxel (60 mg/m²) administered as a 60-min intravenous infusion and/or bevacizumab (15 mg/kg) on day 1 every 3 weeks. Bevacizumab was first intravenously infused over 90 min, and/or bevacizumab (15 mg/kg) on day 1 every 3 weeks. Treatment schedule was determined at the physician’s discretion. Dose reduction was performed in some patients according to the physicians’ judgment. Adequate antibiotics were administered when FN occurred. FN was defined according to the guidelines for Japanese Society of Medical Oncology: axillary body temperature ≥ 37.5°C or oral temperature ≥ 38°C and neutrophil count ≤ 500/µL or current neutrophil count < 1000/µL and expected to fall below < 500/µL during the next 48 h. The use of granulocyte-colony stimulating factor (G-CSF) was permitted as a therapeutic intervention for neutropenia but not for prophylaxis. No patient in the present study received primary prophylactic pegylated-G-CSF. Other medications for underlying diseases, complications, and pain control were allowed.

Clinical Parameters, Data Collection, and Assessment All data were collected from the electronic medical record system. We evaluated information on patients’ sex, age, body weight, Eastern Cooperative Oncology Group-PS (ECOG-PS), chemotherapy history, bevacizumab use, use of medications which have possibility CYP3A-mediated drug interactions with docetaxel, FN occurrence, serum creatinine (Scr) level, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, alkaline phosphatase (ALP) level, total bilirubin (T-Bil) level, leukocyte count, neutrophil count, albumin level, hemoglobin level, and platelet count. These variables were monitored from the beginning of the first course of therapy, and the frequency of laboratory testing was determined at the physician’s discretion. The severity of toxicity was classified according to the Common Terminology Criteria for Adverse Events (CTCAE),

Table 1. Patient Characteristics and FN Frequency (n=81)

| Variable                      | FN    | Non-FN | p-Value |
|-------------------------------|-------|--------|---------|
| Number of patients            | 18    | 63     |         |
| Sex                           |       |        |         |
| Male                          | 15    | 36     | 0.054   |
| Female                        | 3     | 27     |         |
| Age (years)                   | 68.111 ± 8.464 | 67.222 ± 9.056 | 0.711 |
| Body weight (kg)              | 59.048 ± 11.828 | 54.396 ± 11.214 | 0.129 |
| ECOG-PS score                 |       |        |         |
| 0                             | 2     | 26     | 0.018   |
| 1                             | 16    | 32     |         |
| 2                             | 0     | 5      |         |
| Prior chemotherapy            |       |        |         |
| 0                             | 1     | 1      | 0.210   |
| 1                             | 11    | 30     |         |
| ≥2                            | 6     | 32     |         |
| Chemotherapy                  |       |        |         |
| Docetaxel alone               | 14    | 57     | 0.217   |
| Docetaxel + bevacizumab       | 4     | 6      |         |
| CYP3A inhibitors              |       |        |         |
| Yes                           | 0     | 1      | 1.000   |
| No                            | 18    | 62     |         |
| Scr (mg/dL)                   | 0.888 ± 0.199 | 0.820 ± 0.279 | 0.256 |
| AST (IU/L)                    | 26.722 ± 9.922 | 25.556 ± 10.415 | 0.673 |
| ALT (IU/L)                    | 23.500 ± 12.392 | 18.825 ± 9.085 | 0.081 |
| ALP (IU/L)                    | 281.722 ± 239.280 | 323.381 ± 235.580 | 0.519 |
| T-Bil (mg/dL)                 | 0.600 ± 0.307 | 0.457 ± 0.154 | 0.071 |
| Leukocyte count (× 10³/µL)    | 6.261 ± 2.179 | 6.511 ± 2.257 | 0.677 |
| Neutrophil count (× 10³/µL)   | 4.216 ± 2.072 | 4.538 ± 2.071 | 0.563 |
| Albumin (g/dL)                | 3.722 ± 0.433 | 3.716 ± 0.494 | 0.958 |
| Hemoglobin (g/dL)             | 12.817 ± 1.930 | 11.941 ± 1.701 | 0.065 |
| Platelet count (× 10³/µL)     | 20.600 ± 5.944 | 25.121 ± 11.004 | 0.099 |

Values are the number of cases or the mean ± standard deviation (S.D.). a) FN, Febrile neutropenia. b) Values presented in italics have a significant difference (p<0.05) between FN and non-FN groups. c) ECOG-PS, Eastern Cooperative Oncology Group performance status. d) Scr, serum creatinine. e) AST, aspartate aminotransferase. f) ALT, alanine aminotransferase. g) ALP, alkaline phosphatase. h) T-Bil, total bilirubin.
version 5.0. The nadir neutrophil count in each patient was defined as the lowest value during any course of docetaxel chemotherapy. 

**Statistical Analysis** Fisher’s exact tests were used to compare categorical data, as appropriate. Continuous data are presented as mean ± standard deviation (S.D.). Student’s t-tests or Wilcoxon rank-sum tests were used to compare normally distributed variables between groups.

To identify the factors associated with FN, univariate logistic regression analyses were performed including patient sex; age; body weight; ECOG-PS score; prior chemotherapy; and platelet counts as independent variables. Factors with $p < 0.05$ in univariate analyses were evaluated as potential covariates in multivariate stepwise logistic regression analysis with backward selection. The classification performances (specificity and sensitivity) of the candidate factors were also tested by area under the curve (AUC) of the receiver operator characteristic (ROC) curve analysis. Data were analyzed using JMP 13.2.1 (SAS Institute Inc., Cary, NC, U.S.A.), with $p < 0.05$ considered to indicate statistical significance.

**RESULTS**

**Patient Baseline Clinical Characteristics** Eighty-one patients with recurrent or advanced NSCLC were included; 63.0% were males and 37.0% were females. The patients’ demographic data and baseline clinical characteristics are listed in Table 1. No significant differences were observed in sex, age, body weight, prior chemotherapy, CYP3A inhibitors, Scr level, AST level, ALT level, ALP level, T-Bil level, leukocyte count, neutrophil count, albumin level, hemoglobin level, and platelet count between the FN and non-FN groups. However, ECOG-PS score differed significantly between groups ($p = 0.018$).

**Incidence of Neutropenia and FN** Seventy-seven (95.0%) of the 81 patients experienced neutropenia after docetaxel chemotherapy initiation. During the observation period, 24.7 and 58.0% of patients developed grade 3 and 4 neutropenia, respectively, which progressed to FN in 22.2% of these patients. The occurrence frequencies of FN were 29.4% (15 of 51) and 10.0% (3 of 30) in male and female patients, respectively. At a baseline platelet cut-off count of 18.8 × 10^4/µL ($AUC$: 0.652, sensitivity: 50.0, specificity: 81.0%), we observed a significant difference in the occurrence frequency of FN between the patients with baseline platelet counts above and below the cut-off (42.9 and 15.0%, respectively $p = 0.014$). The frequency of FN in patients with an ECOG-PS score of 1–2 was also significantly higher than that in those with ECOG-PS scores of 0 (30.2 and 7.1%, respectively; $p = 0.023$).

**Risk Factors for FN Control** Univariate and multivariate logistic regression analyses were performed to calculate the odds ratios (ORs) of factors influencing the occurrence frequency of FN. Univariate analyses revealed that baseline ECOG-PS scores of 1–2 (OR, 5.622; 95% confidence interval [CI], 1.434–37.499; $p = 0.011$) and baseline platelet count (OR, 0.914; 95% CI, 0.828–0.994; $p = 0.032$) were significantly associated with the incidence rate of FN during docetaxel chemotherapy (Table 2). Variables with $p$-values less than 0.05 were included in the subsequent multivariate logistic regression analysis. Multivariate stepwise logistic regression analysis with backward selection revealed that lower baseline ECOG-PS score of 1 and 2 (OR, 5.098; 95% CI, 1.045–24.879, $p = 0.021$) and baseline platelet count below 18.8 × 10^4/µL (OR, 3.861; 95% CI, 1.211–12.311, $p = 0.022$) were significant factors influencing the occurrence rate of FN (Table 3).

**DISCUSSION**

The present study performed univariate and multivariate logistic regression analyses of data from the Japanese NSCLC patients receiving docetaxel-based chemotherapy to identify risk factors for FN occurrence (Table 3).

Docetaxel alone or in combination with bevacizumab is commonly used in patients with NSCLC, however, this

### Table 2. Risk Factors of FN<sup>a</sup> by Univariate Analysis

| Variables | Odds ratio | 95% Confidence interval | $p$-Value<sup>b</sup> |
|-----------|------------|-------------------------|----------------------|
| Male sex  | 3.750      | 0.986–14.268            | 0.053                |
| Age (years)| 1.012      | 0.954–1.077             | 0.705                |
| Weight (kg)| 1.036      | 0.990–1.086             | 0.131                |
| ECOG-PS<sup>c</sup> 1 and 2 | 5.622 | 1.434–37.499 | 0.011 |
| Prior chemotherapy ≥2 | 0.484 | 0.152–1.411 | 0.186 |
| DTX<sup>d</sup> + Bev<sup>e</sup> chemotherapy | 2.714 | 0.624–10.867 | 0.173 |
| Scr<sup>f</sup> (mg/dL) | 2.534 | 0.353–17.524 | 0.344 |
| AST<sup>g</sup> (IU/L) | 1.011 | 0.962–1.063 | 0.671 |
| ALT<sup>h</sup> (IU/L) | 1.044 | 0.993–1.101 | 0.090 |
| ALP<sup>i</sup> (IU/L) | 0.999 | 0.996–1.001 | 0.484 |
| T-Bil<sup>j</sup> | 3.016 | 0.241–35.704 | 0.374 |
| Leukocyte count (×10^3/µL) | 0.999 | 0.999–1.000 | 0.665 |
| Neutrophil count (×10^3/µL) | 0.999 | 0.999–1.000 | 0.543 |
| Albumin (g/dL) | 1.029 | 0.341–3.102 | 0.960 |
| Hemoglobin (g/dL) | 1.342 | 0.987–1.878 | 0.061 |
| Platelet count (×10^4/µL) | 0.914 | 0.828–0.994 | 0.032 |

<sup>a</sup> FN, Febrile neutropenia. <sup>b</sup> Values presented in italics have a significant difference between groups. <sup>c</sup> ECOG-PS, Eastern Cooperative Oncology Group performance status. <sup>d</sup> DTX, docetaxel. <sup>e</sup> Bev, bevacizumab. <sup>f</sup> Scr, serum creatinine. <sup>g</sup> AST, aspartate aminotransferase. <sup>h</sup> ALT, alanine aminotransferase. <sup>i</sup> ALP, alkaline phosphatase. <sup>j</sup> T-Bil, total bilirubin.
treatment may induce neutropenia as the main dose-limiting toxicity.\textsuperscript{13} FN is one of the most frequent potentially life-threatening complications in patients with NSCLC receiving docetaxel chemotherapy and may require dose reduction or lead to treatment delays, which may potentially compromise the efficacy of chemotherapy.\textsuperscript{18,19} The reported incidence of FN in patients with NSCLC receiving docetaxel-based chemotherapy ranges from 13.4 to 19.8\%.\textsuperscript{20–23} Docetaxel may be used alone or in combination with other anticancer drugs to treat NSCLC. The incidence of FN was reportedly lower than that for docetaxel monotherapy when docetaxel was administered with cisplatin,\textsuperscript{20} amurubicin,\textsuperscript{23} or S-1 containing tegafur, gimeracil, and oteracil.\textsuperscript{22} In contrast, the incidence of FN in patients with advanced NSCLC treated with docetaxel in combination with ramucirumab was higher than that in those receiving docetaxel and placebo.\textsuperscript{21} In the present study, the frequency of FN was 19.7\% in patients treated with docetaxel alone and 40.0\% in those receiving combination therapy of docetaxel and bevacizumab (Table 1).

G-CSF controls neutrophil production and maintains the number of mature and functional neutrophils. Therefore, it is deeply associated with biological defense and is used to treat neutropenia caused by cancer chemotherapy. The American Society of Clinical Oncology guideline recommends the use of G-CSF for patients receiving cancer chemotherapy at high risk for FN.\textsuperscript{24} The National Comprehensive Cancer Network guideline also suggests the routine use of G-CSF in patients with a more than 20\% risk of developing FN or other neutropenic events that would compromise treatment.\textsuperscript{25} As mentioned above, the incidence of FN among patients with NSCLC treated with docetaxel alone and in combination with ramucirumab or bevacizumab is above 20\%; therefore, these patients may require prophylactic administration of G-CSF.\textsuperscript{26} However, dosing lines and G-CSF usage standards vary between clinical trials.\textsuperscript{27} These findings suggest that our present pilot study was limited by its small sample size; therefore, further studies are necessary to investigate the possibility that the addition of anti-VEGF antibodies to docetaxel therapy might increase the frequency of FN occurrence.

Meanwhile, ECOG-PS scores of 1 or 2 before chemotherapy was also a risk factor for FN in NSCLC patients treated with docetaxel (Table 3). These results did not conflict with those reported previously. According to the American Society of Clinical Oncology guidelines, age above 65 years, poor ECOG-PS, advanced-stage cancer, and history of chemotherapy or radiation therapy are risk factors associated with the increased incidence of FN.\textsuperscript{28} Lyman \textit{et al.} summarized the risk factors of FN in patients with various types of cancer and receiving chemotherapy regimens, showing that poor ECOG-PS was an independent risk factor for FN.\textsuperscript{29} Du and co-investigators conducted a systematic review and meta-analysis showing that docetaxel treatment was associated with an increased risk of serious infections in patients with NSCLC.\textsuperscript{30} Ozawa \textit{et al.} identified ECOG-PS scores of 2 or 3 as a significant factor in their logistic regression model to predict the probability of FN occurrence in patients with NSCLC and other types of cancer who received docetaxel-based chemotherapy.\textsuperscript{15} ECOG-PS scores may be categorized as 0–1 and ≥2\textsuperscript{31} or as 0 and ≥1.\textsuperscript{31,32} Additional studies are needed to evaluate these ECOG-PS score divisions. While ECOG-PS scores of 2 and higher have been associated with higher risks of chemotherapy toxicity and poor outcome, some studies have applied a cutoff score between 0 and 1 for analysis.\textsuperscript{20,33–35}

Meanwhile, a lower baseline serum platelet count was also a risk factor for FN in NSCLC patients treated with docetaxel (Table 3). A systematic review of the literature revealed that while a lower platelet count was not previously identified as a significant risk factor for FN,\textsuperscript{29} one report indicated that decreased leukocyte count, neutrophil count, and hemoglobin level were associated with FN in patients with breast cancer who received adjuvant chemotherapy.\textsuperscript{36} Shioita \textit{et al.} reported that severe lymphopenia following docetaxel treatment in patients with castration-resistant prostate cancer may predict FN,\textsuperscript{32} and Lee \textit{et al.} showed that lower platelet count was a prognostic factor in cancer patients developing FN in the emergency department in logistic regression analysis.\textsuperscript{37} A lower platelet count was also a prognostic factor of death in patients with chemotherapy-induced FN and was important for the identification of patients at high risk for FN based on characteristics including lower platelet count, to allow the administration of timely empiric antimicrobial therapy to prevent the development of serious complications and death in patients with FN.\textsuperscript{38,39} Platelets are blood cells that have important functions in host integrity, defense, and repair.\textsuperscript{38} Thrombocytopenia is a frequent symptom when systemic infections are observed.\textsuperscript{38} Thrombocytopenia has been reported to be a risk factor for sepsis.\textsuperscript{40} Meanwhile, neutrophils remove bacterial and fungal pathogens and prevent infection.\textsuperscript{49} Fever in patients with FN may be the only indicator of severe bacterial infection.\textsuperscript{32} The mechanisms associated with baseline platelet counts and the development of FN are unknown. FN occurrence group may have been more susceptible to infection.

In conclusion, our results demonstrated that ECOG-PS 1-2 and a lower baseline platelet count were significant risk factors for FN in patients with NSCLC receiving docetaxel-based chemotherapy. Primary prophylaxis with G-CSF after chemotherapy is recommended for cancer patients with a higher risk of chemotherapy-induced FN. Despite the limitations of this study including its retrospective design, single-center site, and a small sample size, baseline ECOG-PS score and platelet count can be regarded as important indicators to select patients for G-CSF prophylactic treatment before docetaxel-based chemotherapy.

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### Table 3. FN\textsuperscript{a} Risk Factor Analysis by Multivariate Analysis

| Variables                        | Odds ratio | 95\% Confidence interval | \(p\)-Value$^\text{b}$ |
|----------------------------------|------------|--------------------------|------------------------|
| ECOG-PS\textsuperscript{c} 1 and 2 | 5.098      | 1.045–24.879             | 0.021                  |
| Platelet count less than 18.8 (×10\textsuperscript{4}/µL) | 3.861      | 1.211–12.311             | 0.022                  |

\textsuperscript{a} FN, Febrile neutropenia. \textsuperscript{b} ECOG-PS, Eastern Cooperative Oncology Group performance status. \textsuperscript{c} Values presented in italics have a significant difference.
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Conflict of Interest Tomii has received Grants from Sanofi and Chugai and lecture honoraria from Sanofi and Chugai Inc. Other authors declare no conflict of interest.

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