


Can MASCC and CISNE scores predict delays of lung cancer chemotherapy after febrile neutropenia?

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Abstract

Background: Febrile neutropenia (FN) during cancer chemotherapy can lead to morbidity and mortality. The Multinational Association of Supportive Care in Cancer (MASCC) and clinical index of stable febrile neutropenia (CISNE) scores have been widely used to predict the risk of severe medical complications in patients with FN; however, there are few tools for predicting chemotherapy delays or discontinuation after FN.

Methods: Patients admitted to two university hospitals between 2014 and 2018 with a FN diagnosis during the first cycle of chemotherapy for lung cancer were reviewed retrospectively.

Results: Among 539 patients who received 813 courses of chemotherapy for lung cancer, 49 (9%) developed FN during the first treatment cycle. Although all the patients recovered from their primary infection, 19 patients (38.8%) developed serious medical complications, 11 (22.4%) were unable to resume chemotherapy and one (2.0%) declined to resume chemotherapy, and nine (18.4%) died within 90 days. Patients who failed to resume chemotherapy had a lower MASCC score (median 8.5 vs. 17, $p < 0.01$) and a higher CISNE score (median 3 vs. 1, $p < 0.01$) at the onset of FN. The specificity to predict the patient who failed to resume chemotherapy was 90% or more with MASCC score ≤ 9 or CISNE score ≥ 3 , with the sensitivity of 61%. MASCC score ≤ 16 can also be a sensitive indicator with the sensitivity and specificity of 89 and 52%, respectively.

Conclusion: The MASCC and CISNE scores are useful in identifying lung cancer patients who are unable to resume chemotherapy as scheduled after the onset of FN.

KEYWORDS

chemotherapy, complication, febrile neutropenia, prediction, prognosis

INTRODUCTION

Febrile neutropenia (FN) due to cytotoxic chemotherapy is a medical emergency for patients with advanced lung cancer. The incidence of FN during lung cancer chemotherapy varies from a few to more than 20% depending on the regimen, and the mortality rate for patients with lung cancer who develop FN is approximately 11%, which is higher than for patients with other solid tumors.¹ Based on the analysis on University Health Consortium database in United States, patients with lung cancer presenting with FN were older

and had more comorbidities; age ≥ 60 years was an independent risk factor of in-hospital mortality (odds ratio 1.23 [95% confidence interval 1.05–1.44]).¹ Therefore, it is important to assess the risk of FN and apply appropriate interventions for prophylaxis, including granulocyte-colony stimulating factor (G-CSF).^{2–4} Primary prophylaxis with G-CSF reduces the incidence of FN by 9%–50%.^{5–9} Current guidelines of the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) recommend prophylactic use of G-CSF for patients if the risk of FN is $>20\%$ for planned chemotherapy.^{10,11}

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Once patients develop FN, rigorous treatment with broad-spectrum antibiotics and G-CSF is required.¹² There are two widely used scores to predict serious medical complications or death in these patients: Multinational Association of Supportive Care in Cancer (MASCC) score and clinical index of stable febrile neutropenia (CISNE) score.^{13,14} The MASCC score was proposed by Klastersky et al. in 2000 and has been adopted in the ASCO and ESMO guidelines.^{10,11,13,15} Conversely, another prospective study demonstrated that the CISNE score is better for predicting severe FN complications in patients with solid tumors or hematologic malignancies, with an area under the receiver operating characteristic (ROC) curve of 0.868 compared to 0.721 for the MASCC score.¹⁴

MASCC and CISNE scores define serious medical complications as acute respiratory failure, hypotension, acute renal failure, altered mental status, serious bleeding, acute abdomen, arrhythmia, disseminated intravascular coagulopathy, unstable angina, and death.^{13,14} Whether chemotherapy can be resumed without substantial delay after FN is another important endpoint related with the prognosis of patients with lung cancer. Therefore, we examined whether the MASCC or CISNE scores could predict the delay or discontinuation of chemotherapy after an episode of FN in patients with advanced lung cancer.

METHODS

Subjects

We retrospectively reviewed patients admitted to the Tokai University Hospital and Tokai University Hachioji Hospital between January 2014 and June 2018 with FN diagnosed during the first cycle of chemotherapy for advanced lung cancer. Patients who had undergone concurrent chemoradiotherapy were excluded from the analysis. FN was defined as a combination of (1) grade 3 or 4 peripheral blood neutropenia ($\leq 1000/\mu\text{l}$) and (2) a body temperature of $\geq 38.3^\circ\text{C}$ or $\geq 38^\circ\text{C}$ sustained for at least 1 h, according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 with minor modifications:¹⁶ body temperature was measured at the axilla, and not in the oral cavity.

This study was approved by the Institutional Review Boards of the Tokai University Hospital and Tokai University Hachioji Hospital (19R-251 and 19R-314) and implemented in compliance with the Declaration of Helsinki. Informed consent was obtained in the form of an opt-out option on the website. Patients who declined to participate in the study were excluded.

Data collection

We retrospectively reviewed medical records and obtained demographic data, vital signs, and laboratory data prior to

and at the onset of FN. Treatments for FN, duration of fever, and clinical course within 90 days after the onset of FN were also evaluated from the medical charts. Delay of chemotherapy after FN was arbitrarily defined as those who failed to resume chemotherapy within 60 days of the previous treatment.

MASCC and CISNE scores (Table S1)

For the retrospective estimation of the MASCC score¹³ from the medical records, we defined hypotension as systolic blood pressure ≤ 90 mmHg, and diagnosed dehydration if serum creatinine levels increased by 1.5-fold from the basal level or 0.3 mg/dl within 48 h of admission according to the kidney disease: improving global outcomes criteria.¹⁷ We also assumed that there was a severe burden of illness if the patient's consciousness was disturbed, and if not, this was defined as having no or mild burden of illness.

The CISNE score,¹⁴ ranging from 0 to 8, was calculated using the Eastern Cooperative Oncology Group (ECOG) performance status (PS), stress-induced hyperglycemia, chronic obstructive pulmonary disease (COPD), chronic cardiovascular disease, mucositis grade ≥ 2 on the NCI-CTCAE version 4.0, and monocyte count < 200 cells/ μl .

Statistical analysis

Data were presented as medians and interquartile ranges for continuous variables, and numbers and percentages for categorical data. Patients were divided into two groups: those who could resume cancer chemotherapy within 60 days after the onset of FN and those who could not. Group comparisons were made using Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. The sensitivity and specificity were calculated from the ROC curve using the Youden index or the predetermined cutoff values of sensitivity (60%, 70%, 80%).

Statistical analysis was performed using IBM SPSS Statistics software version 26 (IBM). Statistical significance was set at $p < 0.05$.

RESULTS

Among the 539 patients with lung cancer (418 men, median age 72 years) who received 813 courses of chemotherapy, 49 (9.0% per patient, 6.0% per chemotherapy course) developed FN during the first chemotherapy cycle. During first-line ($n = 414$) and second-line or later chemotherapy ($n = 399$), 38 (9.2%) and 11 (2.8%) episodes of FN were reported. The incidence of FN in patients aged ≥ 60 years (9.9%) were significantly higher than patients < 60 years (3.2%, $p < 0.001$). Nineteen patients (38.8%) developed serious medical complications that satisfied the definition of MASCC and CISNE scores. The histology of the lung cancer

TABLE 1 Demographic data and clinical characteristics of patients with febrile neutropenia who could or could not resume chemotherapy

	All (<i>n</i> = 49)	CTx resumed (<i>n</i> = 37)	CTx not resumed (<i>n</i> = 12)	<i>p</i> -value ^a
Age (years)	72 (67–75)	72 (67–75)	70 (68–75)	0.09
Male	42 (86%)	32 (86%)	10 (83%)	0.33
Body mass index	22.2 (20.0–24.2)	22.4 (20.3–24.7)	20.6 (17.8–23.0)	0.53
Smoking history (pack years)	45 (30–56)	45 (36–54)	47 (24–65)	0.22
Non-small cell lung cancer	21 (43%)	11 (30%)	10 (83%)	0.14
Stage IIIA/IIIB/IV, <i>n</i>	9/8/32	8/6/23	1/2/9	0.30
Line of chemotherapy 1/2/3, <i>n</i>	38/9/2	29/7/1	9/2/1	0.11
At chemotherapy				
Leukocyte counts (/μl)	6700 (5700–8200)	7100 (5800–8800)	5800 (5025–7350)	0.19
Neutrophil counts (/μl)	4960 (3800–6480)	5230 (3820–6540)	4800 (2280–5850)	0.91
At the onset of FN				
Leukocyte counts (/μl)	635 (330–932)	702 (497–1068)	377 (249–704)	0.01
Neutrophil counts (/μl)	366 (140–610)	467 (185–701)	310 (134–529)	0.11
C-reactive protein (mg/dl)	6.6 (2.2–12.3)	6.6 (2.2–10.8)	7.1 (2.3–15.7)	0.06
Glucose (mg/dl)	113 (101–130)	110 (101–128)	120 (105–134)	0.04
Days of G-CSF used after FN	5 (3–7)	5 (3–7)	6 (5–7)	0.55

Note: Median (interquartile range).

^aCTx resumed versus CTx not resumed.

Abbreviations: CTx, chemotherapy; G-CSF, granulocyte-colony stimulating factor; FN, febrile neutropenia.

in the patients who developed FN indicated small cell lung cancer in 28 patients and non-small cell lung cancer in 21 patients (Table 1). Among the patients with stage III disease, 17 patients developed FN during chemotherapy alone, in whom chemoradiotherapy had not been performed due to old age (two patients), poor pulmonary function or underlying interstitial lung disease (six patients), too wide a radiation field required to be curative (six patients), and the patient's own will (three patients). The chemotherapy regimens included combination therapy in 41 cases (cisplatin/carboplatin and etoposide [23 cases], cisplatin/carboplatin and irinotecan [seven cases], carboplatin and paclitaxel/nab-paclitaxel [seven cases], docetaxel and ramucirumab [two cases], carboplatin and docetaxel [one case], cisplatin, pemetrexed, and bevacizumab [one case]) and monotherapy in eight cases (docetaxel [four cases], amrubicin [two cases], vinorelbine [one case], pemetrexed [one case]). Five cases of FN (10%) developed in the patients who had received a reduced dose of chemotherapy (80%–90% dose of the standard regimen) due to poor PS and/or co-morbidities. Although one patient received chemotherapy of docetaxel and ramucirumab with a 20% or greater risk of FN in which ASCO and ESMO recommends the use of prophylactic G-CSF,^{10,11} he declined prophylaxis according to the patient's own will. None of the patients under the chemotherapy with less than 20% risk of FN received primary prophylaxis with G-CSF. All patients were treated with G-CSF and antibiotics at the onset of FN.

All the patients with FN recovered from their primary infection after treatment with antibiotics and G-CSF. Thirty-seven patients (75.5%) were able to resume lung cancer chemotherapy within 60 days (median 29 days, IQR 28–35 days); 37 patients restarted chemotherapy within 42 days

except for one who started the treatment at day 43 after previous treatment with cisplatin and irinotecan. However, 11 patients (22.4%) were unable to resume chemotherapy within 60 days due to a decline in PS (*n* = 9) or exacerbation of comorbid lung disease (interstitial lung disease or COPD, *n* = 2), and one patient declined to restart chemotherapy. None of the 11 patients who were unable to resume chemotherapy within 60 days were able to restart any treatment for the cancer except for supportive care; nine of the 12 patients (75.0%), including the one who declined to resume chemotherapy, died within 90 days of FN.

Patients who did not resume chemotherapy within 60 days more frequently exhibited severe burden of illness (consciousness disturbance, *p* < 0.01), hypotension (*p* < 0.01), or dehydration (*p* < 0.01), had lower MASCC score (median 8.5 vs. 17, *p* < 0.01) and higher CISNE score (median 3 vs. 1, *p* < 0.01) at the onset of FN (Table 2). The area under the ROC curve of the MASCC score was 0.84, whereas that of the CISNE score was 0.76 (Figure 1). The Youden score was highest with MASCC and CISNE scores of 9 and 3, respectively (Table 3). The specificity to predict the patient who could not resume chemotherapy was 90% or more with MASCC score ≤ 9 or CISNE score ≥ 3, with the sensitivity of 61%. MASCC score ≤ 16 can also be a sensitive indicator with the sensitivity and specificity of 89 and 52%, respectively (Table 3).

DISCUSSION

In our study, the incidence of FN in the patients with lung cancer treated with cytotoxic anticancer agents was 9.0% per patient or 6.0% per chemotherapy course, which is

TABLE 2 Comparison of MASCC and CISNE scores between patients who could and could not resume chemotherapy

	All (<i>n</i> = 49)	CTx resumed (<i>n</i> = 37)	CTx not resumed (<i>n</i> = 12)	<i>p</i> -value ^b
MASCC score				
Total score ^a	16 (10–17)	17 (12.5–17)	8.5 (8.5–14.5)	<0.01
No or mild burden of illness	21 (43%)	18 (49%)	3 (25%)	<0.01
No hypotension	36 (73%)	28 (76%)	8 (67%)	<0.01
No COPD	19 (39%)	16 (43%)	3 (25%)	0.78
No previous fungal infection	49 (100%)	37 (100%)	12 (100%)	0.99
No dehydration	35 (71%)	28 (76%)	7 (58%)	<0.01
Age < 60 years	2 (4%)	2 (5%)	0 (0%)	0.73
CISNE score				
Total score ^a	2 (2–3)	1 (1–2)	3 (2–3)	<0.01
ECOG PS ≥2	12 (24%)	5 (14%)	7 (58%)	0.06
Stress-induced hyperglycemia	9 (18%)	4 (11%)	5 (42%)	0.68
COPD	30 (61%)	21 (57%)	9 (75%)	0.78
Chronic cardiovascular disease	7 (14%)	6 (16%)	1 (8%)	0.28
Mucositis ≥ NCI-CTCAE grade 2	0 (0%)	0 (0%)	0 (0%)	0.99
Monocyte count <200/μl	39 (80%)	27 (73%)	10 (83%)	0.78

Abbreviations: CISNE score, clinical index of stable febrile neutropenia score; COPD, chronic obstructive pulmonary disease; CTx, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; MASCC score, Multinational Association of Supportive Care in Cancer score; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.

^aMedian (interquartile range).

^bCTx resumed versus CTx not resumed.

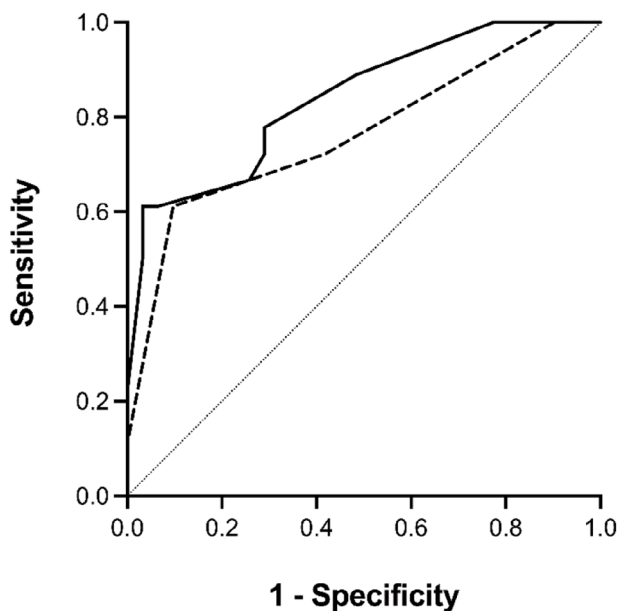


FIGURE 1 Receiver operating characteristic (ROC) curves. ROC curve of Multinational Association of Supportive Care in Cancer score (solid line) and clinical index of stable febrile neutropenia score (dashed line) to predict the resumption of cancer chemotherapy within 60 days after the onset of febrile neutropenia. The line of identity is represented by the dotted line

consistent with previous reports.^{18,19} Among the patients who developed FN, 38.8% developed serious medical complications, 24.5% failed to resume chemotherapy even though all of them had recovered from the primary

infection, and 18.3% died within 90 days. Although a number of studies have aimed to evaluate the risk of FN and FN-related serious medical complications, this is the first study that evaluated the sustainability of chemotherapy after the onset of FN. We found that the MASCC and CISNE scores can predict the discontinuation of the cancer chemotherapy after FN.

Three types of risks are associated with FN during cancer chemotherapy: risk of developing FN, risk of severe illness during FN, and risk of poor outcomes as a sequela of FN. For the risk of FN, a meta-analysis identified older age, lower PS, presence of comorbidities, lower baseline white blood cell count, lower body mass index, and myelosuppressive chemotherapy as risk factors.²⁰ The MASCC and CISNE scores, designed to evaluate the second type of risk, the risk of severe medical conditions during FN, include older age, lower PS, and presence of comorbidities, such as COPD and chronic cardiovascular disease.^{10,12,14} Some studies have tried to evaluate a composite risk, such as the risk of hospitalization due to FN, which is associated with the number of comorbidities, stage of cancer at diagnosis, use of myelosuppressive chemotherapy, and time from diagnosis to first chemotherapy during the first course of chemotherapy for breast, rectal, prostate, and lung cancers.²⁰ These risk evaluation tools are especially useful in emergency departments to identify low-risk patients who can be treated in an outpatient setting.^{21–23}

Severe neutropenia and mucosal damage at the onset of FN, especially in the presence of bacteremia, have been associated with poor prognosis with a high mortality rate of

TABLE 3 Cutoffs for the levels of MASCC and CISNE scores as predictors of not resuming chemotherapy at sensitivities of 80, 70, and 60%

	Cutoff value	Sensitivity	Specificity	Youden index
Sensitivity >80%				
MASCC score	≤16	0.89	0.52	0.41
CISNE score	≥1	1.00	0.10	0.10
Sensitivity >70%				
MASCC score	≤15	0.78	0.71	0.49
CISNE score	≥2	0.72	0.58	0.30
Sensitivity >60%				
MASCC score	≤9	0.61	0.97	0.58
CISNE score	≥3	0.61	0.90	0.51

Abbreviations: CISNE score, clinical index of stable febrile neutropenia score; MASCC score, Multinational Association of Supportive Care in Cancer score.

5–18%.²⁴ The MASCC score is also useful for predicting poor outcomes due to FN, such as septic shock, respiratory failure, need for intensive care, and death.^{25,26} In a study from Turkey, 51/86 patients with MASCC scores <21 died due to FN, whereas only 13 of 114 patients with MASCC scores ≥21 died.²⁵ Another study in the US also demonstrated a higher inpatient death rate in a high-risk group based on the MASCC score (20.8% vs. 2.2%).²⁶ These results are not surprising because the MASCC score includes indicators of circulatory and organ failure, such as hypotension and the presence of dehydration, which are essential for assessing the severity of sepsis.²⁷

On the other hand, no deaths were directly related to FN in the present study. However, lower MASCC scores were still significantly associated with dire consequences, such as the failure to resume cancer chemotherapy and subsequent death. The feature in the target disease may also explain why there was no case with “previous fungal infection”. Severe burden of illness (disturbance of consciousness), hypotension, and dehydration were the components of the MASCC score associated with the failure to resume chemotherapy. COPD was more prevalent in patients who could not resume chemotherapy (75% vs. 57%), although not statistically significant, and one patient could not resume chemotherapy due to COPD exacerbation, suggesting the importance of COPD as a factor in predicting outcomes.

The CISNE score, validated in the prospective FINITE study,²⁸ could also predict the failure to resume cancer chemotherapy, although there was no significant difference in each component between patients who could and could not resume chemotherapy. The patients with ECOG PS ≥2 are less likely to resume chemotherapy after FN. ECOG PS ≥2 is a factor included in the CISNE score, but not in the MASCC score; addition of this component to the MASCC score may improve prediction accuracy. On the other hand, damage to the mucosal barrier and changes in the bacterial flora can cause the development of FN, but are not as frequent in the treatment of lung cancer.²⁹ Given the characteristics of lung cancer patients, it may be useful to make some

modifications to the MASCC and CISNE scores to predict the prognosis of lung cancer chemotherapy patients.

MASCC and CISNE scores evaluate the condition of patients at onset of FN, but not before chemotherapy; therefore, these scores cannot be used to adjust chemotherapy doses. However, identification of the patients with poor prognosis after an episode of FN despite successful treatment of the primary infection would urge the development of better interventions to improve their outcomes, and at minimum provide enough time for patients and families to prepare for a good end of life. Physicians including oncologists tend to overestimate patient survival;^{30–32} these scoring systems which predict prognosis at onset of FN would assist the decision-making process of physicians and patients. At the same time, identification of the indicators that predict poor prognosis prior to chemotherapy and verification of whether dose adjustments of chemotherapy based on these indicators would improve prognosis of patients are important issues to be solved in future studies.

Our study had some limitations. First, it was a retrospective study in two centers. Larger, prospective studies should be performed to identify the appropriate cutoff values for MASCC and CISNE scores to predict the sustainability of cancer chemotherapy after an episode of FN. Second, all the patients with FN were hospitalized in the study according to the protocol of the hospitals, and therefore, the outcomes may be different for the patients managed in an outpatient setting. However, our data are still informative to judge whether the patients with FN should be hospitalized. Third, we have to be careful to interpret our data because they do not demonstrate a direct relationship between FN and death after FN.

In conclusion, the MASCC and CISNE scores were designed to identify low-risk groups of patients who underwent FN during chemotherapy for hematological malignancies and solid tumors. Our data demonstrate that these scores are also useful in identifying lung cancer patients who are unable to resume chemotherapy as scheduled after FN.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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