International Journal of Clinical Oncology (2019) 24:590–595
https://doi.org/10.1007/s10147-018-01384-9

ORIGINAL ARTICLE

c-D-index is a risk factor for prolonged febrile neutropenia during chemotherapy in patients with acute myeloid leukemia

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Received: 27 June 2018 / Accepted: 19 December 2018 / Published online: 2 January 2019

Abstract

Background D-index is a recently established clinical tool for assessing neutropenia severity. This study examined whether the D-index can predict the onset of various infections in patients with febrile neutropenia (FN).

Methods We retrospectively investigated FN events in consecutive patients aged < 65 years who were treated for newly diagnosed acute myeloid leukemia at our institution. We collected data on all FN events during chemotherapy and evaluated the association of FN severity with infectious events. Results: This study included 35 patients (18 women and 17 men; median age, 51 years [range 18–65 years]) with 122 FN events. The response rate to induction chemotherapy was 60% (21/35), and all but one patient survived the treatment. The D-index did not predict FN onset. However, in multivariate analysis, high-dose cytarabine and total D-index were statistically significant explanatory factors for microbiological-proven infections. In addition, multivariate analysis showed that diabetes mellitus is the only risk factor for FN onset. Furthermore, older age, consolidation therapy, and cumulative D-index (c-D-index) were risk factors for prolonged FN. The FN period was the longest in patients with respiratory infections.

Conclusion The D-index did not predict the onset of infection. However, FN duration might be prolonged during consolidation therapy in elderly patients with diabetes mellitus, and it is important to manage respiratory infections. These findings indicate the c-D-index is a useful tool to predict prolonged FN.

Keywords Acute myeloid leukemia · Consolidation chemotherapy · D-index · Febrile neutropenia · Induction chemotherapy · Invasive fungal infection

Abbreviations

AML	Acute myeloid leukemia
c-D-index	Cumulative D-index
ECOG	Eastern Cooperative Oncology Group
FAB	French–American–British
FN	Febrile neutropenia
JALSG	Japan Adult Leukemia Study Group
L-index	Lymphocyte index
PS	Performance status

Background

Prolonged neutropenia is known to carry a high-risk for severe infections, such as pneumonia and bloodstream infections, particularly in patients undergoing chemotherapy for hematological malignancies [1]. The D-index, which was originally proposed as a quantitative parameter to assess neutropenia severity by Portugal et al. [2], is calculated by plotting the daily neutrophil count during the neutropenic period and measuring the area between the curve and the line representing 500 neutrophils/μL. Thus, the D-index evaluates the accumulated deficit of the neutrophil counts < 500 cells/μL over the neutropenic period. The D-index was recently investigated as a potential predictor of infections resulting from neutropenia [2–6].

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Previous reports evaluated the D-index's efficacy in predicting opportunistic infections. The original study by Portugal et al. evaluated the efficacy of the cumulative D-index (c-D-index), defined as the D-index from the start of grade 4 neutropenia until the onset of febrile neutropenia (FN), as a predictor for invasive fungal infections [2]. Their analysis showed that a c-D-index value exceeding 5800 was strongly correlated with the onset of invasive fungal infections, with sensitivity and specificity of 91% and 58%, respectively, in patients with acute myeloid leukemia (AML) undergoing induction chemotherapy. A subsequent report [3] showed that c-D-index values more than 5500 predicted pulmonary infections after stem cell transplantation; although the positive predictive value was only 31.5%, the negative predictive value was 97.4%. However, two subsequent clinical studies failed to show that the c-D-index can predict development of pulmonary infections during consolidation chemotherapy with high-dose cytarabine [4] or after reduced-intensity stem cell transplantation [5]. More recently, a similar evaluation of the lymphocyte index (L-index) during chemotherapy reported that the D-index was superior to the L-index for screening populations at risk for pulmonary infections [6].

Accumulating evidence supports the relevance of the D-index to invasive fungal infections in patients with hematologic malignancies. However, these patients are predisposed to FN, and an index that only predicts pulmonary infections is not ideal. Therefore, this study aimed to identify risk factors contributing to FN onset, considering several factors related to the D-index: c-D-index, total D-index, and total c-D-index. We also investigated the association between the D-index and fever duration, and differences in D-index between different infection foci.

Subjects and methods

Study design and eligibility criteria

This retrospective study included consecutive AML patients treated at our institution between November 1998 and February 2015. The inclusion criteria were age, 18–64 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) score, 0–2; hematological diagnosis, de novo AML; treatment, the Japan Adult Leukemia Study Group (JALSG) 97 [7] or 201 [8] protocol regimens. Patients with poor performance status (PS score ≥ 3) at the time of diagnosis and those with acute promyelocytic leukemia (French–American–British [FAB] classification, M3) were excluded.

Treatment regimens

The induction chemotherapy regimen consisted of 12 mg/m^2 idarubicin daily for 3 days or 50 mg/m^2 daunorubicin daily for 5 days, combined with 100 mg/m^2 cytarabine daily for 7 days. The consolidation chemotherapy consisted of three cycles of high-dose cytarabine at 2 g/m^2 twice a day for 5 days. Alternatively, four courses of consolidation therapy were used as follows: (1) first consolidation, cytarabine 200 mg/m^2 daily for 5 days and mitoxantrone 7 mg/m^2 for 3 days; (2) second consolidation, cytarabine 200 mg/m^2 daily for 5 days and daunorubicin 50 mg/m^2 daily for 3 days; (3) third consolidation, cytarabine 200 mg/m^2 daily for 5 days and aclarubicin 20 mg/m^2 daily for 5 days; and (4) final consolidation, cytarabine 200 mg/m^2 daily for 5 days, etoposide 100 mg/m^2 daily for 5 days, vincristine 0.8 mg/m^2 on day eight, and vindesine 2 mg/m^2 on day 10.

Definition of FN

FN was defined as a fever ≥ 38 °C with a neutrophil count < 500 cells/μL. A fever ≥ 38 °C after a reduced body temperature of < 37.5 °C for > 48 h was defined as a new FN event. All FN events, from the start of the induction chemotherapy (or first chemotherapy at our institution) to the end of the final consolidation therapy, were collected by a chart review.

Definitions of the Indices

Figure 1 shows the schematic illustration of the indices investigated in the present study. The D-index was calculated as the area between the neutrophil curve during grade 4 neutropenia and the line representing 500 neutrophils/μL. The c-D-index was the cumulative D-index calculated from the start of grade 4 neutropenia to FN onset; the c-D-index was equal to the D-index without FNs. The total c-D-index was calculated from the first chemotherapy to FN onset, and the total D-index was calculated from the first to the final chemotherapy; these indices evaluated the additive effects of neutropenia.

Diagnosis of infectious disease

Infectious disease diagnosis was based on the following criteria: (1) positive identification of the causative organism (bacterium or fungus) from aseptically collected clinical specimens, (2) isolation of a pathological organism (bacterium or fungus) that could cause clinical manifestations, or (3) strong suspicion of an infectious disease based on the patients' clinical course and symptoms of, supported by specific serum markers for infection, such as β-D-glucan and procalcitonin. We comprehensively categorized the patients' clinical symptoms into five infection foci based on their clinical manifestations and culture results: oral cavity (stomatitis, toothache, and gingivitis), gastrointestinal tract (nausea, vomiting, diarrhea, and abdominal pain), respiratory tract

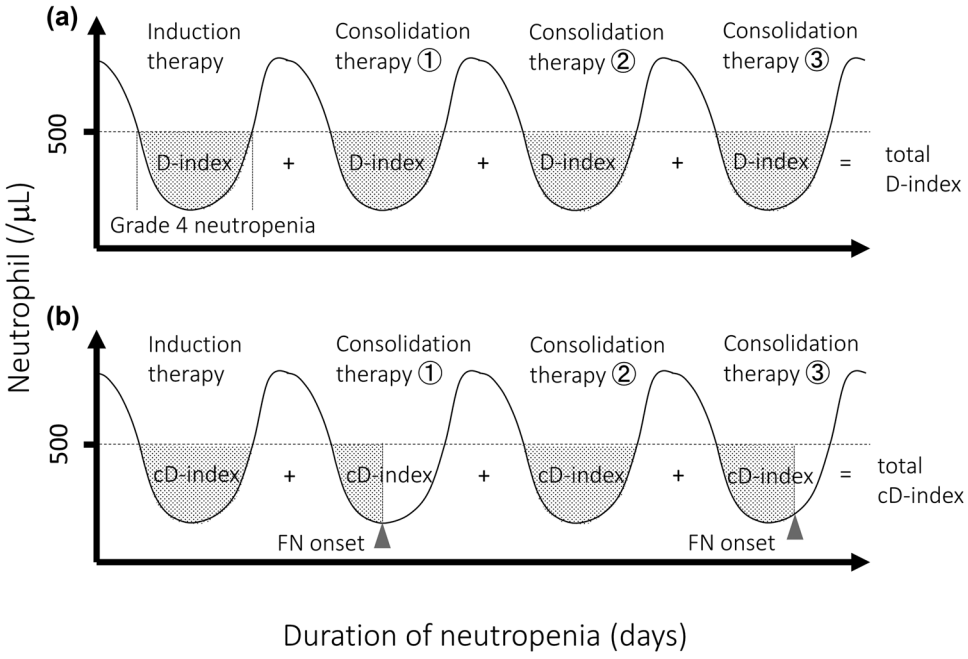

Fig. 1 Definitions of the four indices investigated in this study. The D-index, total D-index, cumulative D-index (c-D-index), and total c-D-index are shown on the neutrophil count curve of a representative patient undergoing induction therapy and three cycles of consolidation therapy. *FN* febrile neutropenia

(cough, sputum, dyspnea, and chest pain), skin (rash, swelling, flare, and pain, including at the site of device insertion), bloodstream (positive blood culture in the absence of clinical manifestations), and unknown origin (negative blood culture in the absence of clinical manifestations or the coexistence of multiple clinical manifestations that could be differentiated from other diagnoses).

Statistical analysis

We used basic statistics to describe representative patient characteristics. Two-tailed paired Student's *t* test was used for parametric analyses. The Chi-squared test was used for nonparametric analyses of values between the groups. Univariate analysis was used to establish explanatory factors for clinical outcomes, including FN onset, overt infection, focus of infection, and fever duration. Multivariate analysis was used to identify risk factors contributing to the onset of FN or duration of FN, potentially including the D-index and related indices. We performed subgroup analyses for each infection focus. We also evaluated the association of D-index and fever duration and the difference in D-index values at each infection focus. In the multivariate analyses, we evaluated patient background factors (age, sex, chemotherapy regimen, and comorbidities) as independent variables and the onset or duration of FN as dependent variable using the regression model. A stepwise selection procedure was used to build the multivariable logistic regression model using the above background risk variables. The entry criterion was set at $P < 0.15$. Statistical significance was defined at $P < 0.05$. Statistical analyses were performed using SPSS version 19.0J software (SPSS Japan, Tokyo, Japan).

Results

Thirty-five patients (18 women and 17 men) with a median age of 51 years (range, 18–65 years) met the eligibility criteria. The study cohort had 122 FN events, including 37 and 74 events occurring in the induction and consolidation chemotherapy episodes, respectively. The patient distribution based on the FAB classification was as follows: M0, $n = 1$; M1, $n = 5$; M2, $n = 14$; M4, $n = 3$; M5, $n = 3$; M6, $n = 2$; and secondary AML, $n = 7$. Patient characteristics are presented in Table 1. Based on the JALSG prognosis score, 12, 13, 9, and 1 patient had good, intermediate, poor, and unknown risks, respectively. The response rate to induction chemotherapy was 62.9% (22/35), and 97% (34/35) of patients were alive at the end of the follow-up period, with only one death during chemotherapy due to *Stenotrophomonas maltophilia* (patient number 24).

In the univariate analysis of risk factors for FN onset, high-dose cytarabine, consolidation therapy, diabetes mellitus, c-D-index, total c-D-index, and total D-index were identified as risk factors (Table 2). High-dose cytarabine was a statistically significant explanatory factor for microbiologically proven infections ($P = 0.0018$). Multivariate analysis revealed that diabetes mellitus as a comorbidity was the only risk factor for FN onset (Table 3), whereas older age, consolidation therapy, and c-D-index were risk factors for prolonged FN duration (Table 4). The chemotherapy

Table 1 Patient characteristics

Age (years)	Median	51
	Range	18–65
Sex	Male	17
	Female	18
JALSG risk	Good	12
	Good-intermediate	1
	Intermediate	8
	Intermediate-poor	4
	Poor	8
	Unknown	2
FAB classification	M0	1
	M1	5
	M2	15
	M4	3
	M6a	3
	M5b	0
	M6a	4
	M7	0
	Unknown	4
Diabetes mellitus	(+)	7
	(−)	28
Smoking history	(+)	12
	(−)	18
	Unknown	5
History of corticosteroid treatment	(+)	0
	(−)	35
Prophylaxis for bacterial infection	(+)	30
	(−)	5
Induction therapy	IDR + Ara-C	28
	DNR + Ara-C	4
	Unknown	3
Re-induction therapy	IDR + Ara-C	6
	DNR + Ara-C	1
	Others	1
	(−)	27
Consolidation therapy	High-dose Ara-C	22
	Anthracycline + Ara-C	6
	Unknown	7

JALSG Japan Adult Leukemia Study Group, *FAB* French–American–British classification, *IDR* idarubicin, *Ara-C* cytarabine, *DNR* daunorubicin

response rates were 69.2% (9/13), 83.3% (10/12), and 30.0% (3/10) among the good-, intermediate-, and poor-risk patients, respectively. The prevalence rates of FN in the good-, intermediate-, and poor-risk groups were 61.5% (8/13), 58.3% (7/12), and 80.0% (8/10), respectively, indicating that complete response and FN rates were inversely associated with the risk status, but it was not statistically significant ($P = 0.523$). Subsequently, the FN incidence was 68.2% (15/22) and 61.5% (8/13) with and without complete response, respectively ($P = 0.689$, not statistically significant). Conversely, FN onset occurred on days 13 (range 4–18), 9 (range 6–19), and 10 (range 2–18) in the good-, intermediate-, and poor-risk groups, respectively, which were not significantly different among the risk groups. In addition, the FN duration was 13 (range 1–19 days), 10 (range 8–20 days), and 11 days (range 3–19 days) in the good-, intermediate-, and poor-risk groups, respectively, which were not significantly different among the risk groups.

The FN period was the longest among patients with respiratory infections (Fig. 2). The most common pathogens were *Streptococcus mitis, Klebsiella pneumonia*, and *Escherichia coli*, which were isolated in 7, 3, and 2 episodes, respectively. The D-index did not predict infection onset. However, multivariate analysis showed that high-dose cytarabine regimen and total D-index were statistically significant factors contributing to the infection onset ($P = 0.0009$ and 0.0205, respectively).

Discussion

Our analyses revealed only diabetes mellitus as a risk factor for FN onset. The c-D-index, albeit not associated with FN onset, was an independent risk factor for FN duration, as were older age and undergoing consolidation therapy. The study patients' treatment regimens included the JALSG AML97 protocol, in which the consolidation therapy included four courses of combination chemotherapy with cytarabine and anthracycline rotation, and the JALSG AML201 protocol, in which the consolidation therapy included three courses of high-dose cytarabine. Furthermore, high-dose cytarabine was significantly associated with proven infection.

FN onset may be confounded by concomitant diabetes mellitus, which is associated with poor hygiene of certain sites in some patients, such as poor oral hygiene and foot–skin erosion. Indeed, the prevalence of infection at such sites among diabetic patients tends to be higher than that among non-diabetic patients, implying diabetes mellitus as a universal risk factor for febrile episodes due to infection, including FN [9]. Diabetes mellitus was previously reported as a marginal risk factor for FN [10]. In a study of patients with head and neck cancer, tube feeding and diabetes mellitus were contributing risk factors for FN in multivariate analysis [11]. We assessed comorbidities, such as diabetes mellitus, smoking history, and corticosteroid treatment, as independent variables to predict FN onset for several reasons. First, smoking was reported as a risk factor for FN treatment failure in an outpatient clinic setting [12]. In addition, corticosteroid use can modify and obscure the signs and symptoms of infection [13] and was, therefore, included

Table 2 Risk factors for the onset of febrile neutropenia

Contributing factor		*P* value
Patient characteristics	Age	0.4778
	Sex	0.4635
Chemotherapy regimen	High-dose Ara-C	0.0004*
	Consolidation therapy	0.0021*
Comorbidity	Diabetes mellitus	0.0109*
Clinical data	Absolute neutrophil count at the start of chemotherapy	0.2882
	Absolute neutrophil count at the onset of febrile neutropenia	0.5171
	The day of the onset of febrile neutropenia	0.4879
	D-index	0.0784
	c-D-index	0.0448*
	Total c-D-index	0.0489*
	Total D-index	0.0471*
	Duration of fever	0.4550

Univariate analysis identified that high-dose Ara-C regimen, consolidation therapy, diabetes mellitus, c-D-index, total c-D-index, and total D-index were contributing factors to the onset of febrile neutropenia

Ara-C cytarabine, *c-D-index* cumulative D-index

**P* values < 0.05 were considered statistically significant

Table 3 Risk factors for the onset of febrile neutropenia

Contributing factor		*P* value
Patient characteristics	Age	0.9708
	Sex	0.2912
Comorbidity	Diabetes mellitus	0.0193*

Multivariate analysis identified diabetes mellitus as a contributing factor to the onset of febrile neutropenia

**P* values < 0.05 were considered statistically significant

Table 4 Risk factors for the duration of febrile neutropenia

Contributing factor		*P* value
Patient characteristics	Age	0.0455*
	Sex	0.0666
Chemotherapy regimen	Consolidation therapy	0.0190*
Comorbidity	Diabetes mellitus	0.4442
Clinical data	c-D-index	0.0378*

Multivariate analysis identified age, consolidation therapy, and c-D-index as contributing factors to the duration of febrile neutropenia

c-D-index cumulative D-index

**P* values < 0.05 were considered statistically significant

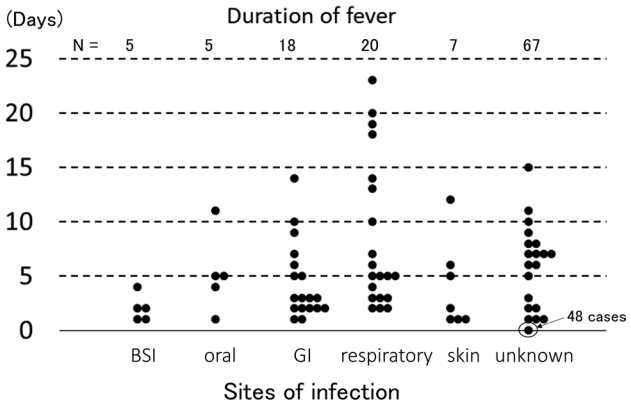

Fig. 2 Comparison of fever duration among infectious sites. The fever was longest in patients with respiratory infections (average, 8.5 days; range, 2–23 days). *BSI* bloodstream infection, *GI* gastrointestinal infection

as a potential risk factor in the present study. Detecting the infection focus and the causative pathogen in FN patients is challenging. Conversely, microbiologically confirmed infections were shown to be more prevalent in elderly patients treated with high-dose cytarabine [14], which is a known risk factor due to chemotherapy-induced mucosal damage [14]. A recent study reported that the prevalence of invasive fungal infections in patients treated with high-dose cytarabine was higher than that in those receiving other consolidation therapy regimens [15]. Finally, we presumed the disease status and response rate to chemotherapy might be associated with FN (i.e.,., onset and duration). In our study cohort, patients with good risk have lower risk of FN than those with poor-risk. However, this tendency was not statistically significant. Moreover, the incidence of FN did not differ between patients who achieved complete remission and those who did not.

In the subgroup analyses based on the infection focus, FN duration was longest in patients with respiratory infections. For infection sites with long FN durations, the D-index could predict FN episodes. The infection focus

sites most prone to FN episodes remain an unsettled clinical question [16]. We speculated that the sensitivity to FN may differ among infection sites because of differences in the mucosal vulnerability to pathogens and the antimicrobial distribution at each tissue site, which requires further investigation.

This study has limitations, including lack of data pertaining to the antibiotics, single-institution study design, and the small number of patients. However, this was the first study to analyze risk factors associated with neutropenia severity and duration among AML patients during induction and consolidation chemotherapy. The subgroup analysis based on the infection site was a novel approach and potentially beneficial for the clinical management of FN. Further investigation of the relationship between the infection site and FN is necessary to confirm the results.

Conclusions

This retrospective analysis revealed that total c-D-index and c-D-index could predict FN onset, and high-dose cytarabine treatment was a poor-risk factor for microbiologically proven overt infection. Older age, consolidation therapy, and c-D-index were risk factors for prolonged FN.

Author contributions OI and HK managed the patient cases, contributed to the literature search, and wrote the manuscript. YHK made substantial contributions to the concept and design of this report. MU qualified the patient data, suggested important intellectual content. YHK and MU took part in critical discussions. NK was involved in supervision of the manuscript and managed the research. All authors approved the final version of the manuscript.

Funding The authors declare that there are no funding sources to disclose concerning to this study, which was supported by internal funding.

Data Availability The datasets used and analyzed in the present study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Ethics approval Institutional review board approved the clinical study and submission of medical literature.

Ethics, consent, and permissions We have obtained consent to participate under our institutional review board.

Consent to publish We have obtained consent to publish from the participant.

Conflict of interest The authors declare that they have no competing interests.

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