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Screening for dental focal infections in febrile patients with hematologic malignancies who received chemotherapy: a retrospective cohort study

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Abstract: Source of fever in chemotherapy patients is often unknown. Fever can also be fatal. No observational studies have determined the incidence of dental focal infection (DFI)-associated fever, despite oral cavity being a potential source of infection. We report the incidence of fever after chemotherapy in patients with hematological malignancies and their association with DFIs in 441 patients visiting our institution during a 6-year period. Dental treatments, including tooth extraction, were performed, and their oral and hematological profiles were monitored after chemotherapy. Fever was evident in 87 (38.5%) of 226 patients (≥ 38˚C) after the first cycle of chemotherapy. Sepsis due to DFIs (n = 4; 4.6%) was evaluated. Chemotherapy was delayed due to DFI in one case. Fever after chemotherapy should be differentiated from oral infections. Our study emphasizes the significance of DFI in patients with fever after chemotherapy and can help in improving the prognosis of patients.

***Keywords*:** fever, hematopoietic neoplasm, immunosuppression, infection, oral cavity

Patients with hematologic malignancy are susceptible to infections due to myelosuppression during their chemotherapy regimen (*1,2*). Fever is a frequent adverse event associated with chemotherapy and often represent the only clinically evident sign of a serious infection in these immunocompromised patients (*3*). Although early identification of the etiology of fever and administration of appropriate treatment are essential, because fever can sometimes lead to death even without a clear cause of fever (*4*), particularly in patients with myelosuppression. However, establishing a precise and early diagnosis is challenging (*5,6*). The oral cavity is a potential site for infection, and dental focal infections (DFIs), such as periodontitis and pericoronitis, have been reported to cause life-threatening systemic morbidities (*7,8*). However, no observational study has adequately followed and investigated the incidence of DFI-associated fever and potential oral factors that affect the chemotherapy schedule in patients with hematologic malignancies.

We conducted a study to examine the incidence of fever after chemotherapy and emphasize the importance of intraoral evaluation in patients with hematologic malignancies who need chemotherapy. This is a retrospective cohort study using medical records obtained from the Department of Oral and Maxillofacial Surgery of our institution. We selected patients with hematologic malignancies, such as multiple myeloma, malignant lymphoma, myeloid/lymphoid leukemia, and myelodysplastic syndrome, who received chemotherapy at the Department of Hematology of our institution from January 2011 to December 2016. To avoid duplication of target patients, we excluded patients who received chemotherapy before the study period. In the included patients, we investigated the incidence of fever; predicted sources of fever, including DFIs that were reported in their medical records; and their adverse impact on chemotherapy schedule. Additionally, we examined the duration from fever onset to the diagnosis of the etiology of fever and analyzed the differences using regression analysis. The observation period for each patient was 30 days from the initiation of first cycle of antineoplastic chemotherapy. Patients with inadequate follow-up were excluded. In the present study, fever was defined by an axillary temperature of ≥ 38˚C.

In total, 441 patients with hematologic malignancies visited our institution during the study period. After

exclusion, we identified 226 patients (133 men, 58.8%; 93 women, 41.2%) with a median age of 65 (range, 16-93) years at first visit to our department. All patients received oral health care and appropriate dental treatments, including tooth extraction (n = 82, 36.3%), before chemotherapy. The most common hematologic diagnosis was malignant lymphoma (n = 116, 51.3%), followed by multiple myeloma (n = 53, 23.5%), myeloid/lymphoid leukemia (n = 41, 18.1%), and myelodysplastic syndrome (n = 16, 7.1%). Among these patients, 87 (38.5%) experienced fever (≥ 38˚C) after chemotherapy (Table 1), including fever of unknown origin (FUO) (n = 19, 21.8%), febrile neutropenia without evidence of infection (FN) (n = 17, 19.5%), tumor-related fever (n = 17, 19.5%), drug-related fever (n = 9, 10.3%), and systemic bacterial or viral infection (n = 25, 28.7%). The most frequently observed causes of systemic infection were catheter-related blood stream infection and pneumonia (n = 6, 6.9%). Sepsis due to DFIs (n = 4, 4.6%), such as pericoronitis of the wisdom tooth (n = 1), acute marginal periodontitis (n = 1), and surgical site infection (SSI) associated with tooth extraction (n = 2), were also observed (Table 2). The difference in the time taken to diagnose infection-associated fevers could not be analyzed due to the small sample size; in three of the four DFI-associated patients who experienced fever, approximately two weeks were needed to diagnose the cause of fever (1, 13, 15, and 27 days, respectively). Furthermore, in one patient, chemotherapy was postponed because of SSI associated with tooth extraction. No significant difference was noted in the number of patients with fever who underwent tooth extraction and those who did not (58 cases, 66.7%, and 29 cases, 33.3%, respectively; p = 0.48 by two-tailed t-test).

Although the importance of screening for infection before initiating chemotherapy has long been recognized, dental-medical cooperation and sharing of relevant information between dental and medical staff can be improved further (*7*). Our hospital follows a clinical protocol to identify potential sources of infection in the stomatognathic region in patients with hematologic malignancy scheduled to receive their first cycle of chemotherapy. This protocol enabled us to record and track the incidences of oral adverse events after chemotherapy; this benefit indicates that medical cooperation between the departments of dentistry and hematology is extremely valuable to improve the treatment outcome of patients with hematologic malignancies.

We report that fever (≥ 38˚C) occurred within 30 days from the first cycle of antineoplastic chemotherapy

Table 1. Distribution of hematologic diagnosis and febrile patients after chemotherapy

Hematologic diagnosis	Male	Female	Total	No. of patients with fever	95% CI
Malignant lymphoma	63	53	116	33 (28.4%)	20.5-37.6
Multiple myeloma	31	22	53	16 (30.2%)	18.3-44.3
Myeloid/lymphoid leukemia	26	15	41	31 (75.6%)	59.7-87.6
Myelodysplastic syndrome	13	3	16	7 (43.8%)	19.8-70.1
Total	133 (58.8%)	93 (41.2%)	226	87 (38.5%)	32.1-45.2

CI, confidence interval.

Table 2. Details of infection-associated fever sources and adverse impact on the chemotherapy schedule

Infection-associated fever sources	No. of patients[*1]	%	Duration required for diagnosis of the fever source[*2]	No. of patients with chemotherapy delay
			Mean ± S.D. (Range) (days)	
Catheter-related blood stream infection	6	6.9	3.83 ± 4.75 (1, 13)	0
Pneumonia	6	6.9	2.67 ± 1.51 (1, 5)	0
Dental focal infection	4	4.6	14.00 ± 10.65 (1, 27)	0
SSI associated with tooth extraction	(2)	2.3	20.00 ± 9.90 (13, 27)	1
Acute marginal periodontitis	(1)	1.1	1	0
Pericoronitis of the wisdom tooth	(1)	1.1	15	0
Pharyngitis	4	4.6	4.75 ± 5.56 (1, 13)	1
Urinary tract infection	2	2.3	1.50 ± 0.71 (1, 2)	0
Upper respiratory infection	1	1.1	4	0
Viral hepatitis	1	1.1	13	0
Peritonsillar abscess	1	1.1	12	0
Total	25/87 (28.7%)		5.92 ± 6.56 (1, 27)	2

[*1] ( ) shows the number of patients with dental focal infection; [*2] Duration from the day of fever onset to the day of final diagnosis of fever sources. SSI, surgical-site infection.

in approximately 40% patients with hematologic malignancies. Notably, among the patients who developed fever after chemotherapy, nine (10.3%) were presumably caused by head and neck infections and approximately 5% patients experienced fever because of DFIs; moreover, chemotherapy was postponed because of fever in one patient. To our best knowledge, this is first report to investigate the incidence of DFI in febrile patients with hematologic malignancies who required chemotherapy.

In this study, one patient exhibited acute periodontitis with fever after initiation of chemotherapy; early diagnosis was possible because of severe cellulitis in the buccal region that was evident visibly. In contrast, the diagnosis was late in the other three patients; this included one case of delayed chemotherapy because the possibility of oral cavity-related problem was not initially listed as an option. Tooth extraction before chemotherapy not only helps to extract decayed tooth and treat periodontitis, it also helps in eliminating the DFIs in patients anticipated to experience myelosuppression (*9*). The patient in whom chemotherapy was delayed underwent tooth extraction to remove the infected foci against chronic apical periodontitis of the mandibular first molar approximately 2 weeks before chemotherapy; follow-up was terminated temporarily before initiating chemotherapy because no tooth extraction-related adverse events were observed and the patient could self-administer oral health care. However, fever developed 2 days after initiation of chemotherapy with a sudden decline of physical strength; therefore, the second cycle of chemotherapy was postponed for approximately one week because of prolonged sepsis caused by late onset SSI associated with tooth extraction. Fortunately, the sepsis symptoms were relatively mild and did not affect the chemotherapy schedule in other patients with tooth extraction-associated SSI and pericoronitis. However, these symptoms may hinder administration of chemotherapy because oral hygiene was extremely poor in the affected patients and a severe infection was suspected because of whole-body weakness that accompanied chemotherapy. Based on these observations, we suggest that long-term follow-up (at least during chemotherapy administration) should be performed for patients undergoing tooth extraction, even if the surgical site indicates a good prognosis. Additionally, oral cleaning should be performed regularly even after initiating chemotherapy.

This study had several limitations. First, DFI-associated fever may have been present in patients with FUO. Previously, many reported cases have been diagnosed as FUO after chemotherapy and have demonstrated progression without a clear etiology (*10*). In our study, 21.8% patients who experienced fever were diagnosed with FUO. Among them, definitive intraoral findings were only available in 7/19 (36.8%) patients who visited our department; possibly, many of the patients with FUO may have had DFI. Second, in our study, DFI-related sepsis was not proven bacteriologically; diagnosis was established based on clinical findings. Although the sequential organ failure assessment score is used for the diagnosis of sepsis, detection of microorganisms in blood culture is not essential (*1*). Blood cultures are frequently obtained in patients with serious infections, and they play an important role in identifying the source of infection. In this study, blood cultures were negative in all four cases of DFI-associated sepsis; however, from the clinical findings, the oral cavity was identified as the source of the infection. According to a previous study, of the 1,015 patients with fever (≥ 38˚C), only 128 (12.6%) had clinically significant positive blood cultures, excluding contamination (*11*), indicating that even in patients with sepsis, the causative microorganism cannot always be detected by blood culture. These observations suggest that comprehensive assessments based on clinical findings, including oral and maxillofacial regions, are needed to identify whether an infection reflects fever even if the blood culture results are negative.

Although fever has been usually regarded as a sign of infection (*10*), many types of fever may occur without infection, such as FUO, FN, tumor-related fever, and drug-related fever (*10,12-15*); these were also analyzed in this study. Because differential diagnosis of the etiology of fever after chemotherapy is diverse in patients with hematologic malignancies, further investigation of each symptom is necessary.

In conclusion, although systemic morbidity caused by DFIs is rare, medical and dental specialists should closely monitor oral infections in patients with hematologic malignancy undergoing chemotherapy manifesting fever with unclear source.

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Ethical Approval

All investigations were performed according to the protocols that were reviewed and approved by the ethical committee of National Center for Global Health and Medicine (NCGM-G-001791-02); the requirement for informed consent was waived because of the retrospective study design. We also conducted in accordance with the tenets of the Declaration of Helsinki.

References

1. Greenberg JA, David MZ, Churpek MM, Pitrak DL, Hall JB, Kress JP. Sequential organ failure assessment

score modified for recent infection in patients with hematologic malignant tumors and severe sepsis. Am J Crit Care. 2016; 25:409-417.
2. Benoit DD, Vandewoude KH, Decruyenaere JM, Hoste EA, Colardyn FA. Outcome and early prognostic indicators in patients with a hematologic malignancy admitted to the intensive care unit for a life-threatening complication. Crit Care Med. 2003; 31:104-112.
3. Patel DM, Riedel DJ. Fever in immunocompromised hosts. Emerg Med Clin North Am. 2013; 31:1059-1071.
4. Vanderschueren S, Eyckmans T, De Munter P, Knockaert D. Mortality in patients presenting with fever of unknown origin. Acta Clin Belg. 2014; 69:12-16.
5. McCarthy PL. Fever without apparent source on clinical examination. Curr Opin Pediatr. 2004; 16:94-106.
6. Slater M, Krug SE. Evaluation of the infant with fever without source: an evidence based approach. Emerg Med Clin North Am. 1999; 17:97-126.
7. Akashi M, Shibuya Y, Kusumoto J, Furudoi S, Inui Y, Yakushijin K, Okamura A, Matsuoka H, Komori T. Myelosuppression grading of chemotherapies for hematologic malignancies to facilitate communication between medical and dental staff: lessons from two cases experienced odontogenic septicemia. BMC Oral Health. 2013; 13:41.
8. Meurman JH, Pyrhönen S, Teerenhovi L, Lindqvist C. Oral sources of septicaemia in patients with malignancies. Oral Oncol. 1997; 33:389-397.
9. Shimada Y, Nakagawa Y, Ide K, Sato I, Hagiwara S, Yamada H, Kawasaki Y, Maruoka Y. Importance of eliminating potential dental focal infection before the first cycle of chemotherapy in patients with hematologic malignancy. Support Care Cancer. 2017; 25:1379-1381.
10. Engelhart S, Glasmacher A, Exner M, Kramer MH. Surveillance for nosocomial infections and fever of unknown origin among adult hematology-oncology patients. Infect Control Hosp Epidemiol. 2002; 23:244-248.
11. Stryjewski ME, Kanafani ZA, Chu VH, Pappas PA, Harding T, Drew LA, Benjamin DK Jr, Reller LB, Lee BA, Corey GR, Fowler VG Jr. Staphylococcus aureus bacteremia among patients with health care-associated fever. Am J Med. 2009; 122:281-289.
12. Zakhour R, Chaftari AM, Raad II. Catheter-related infections in patients with haematological malignancies: novel preventive and therapeutic strategies. Lancet Infect Dis. 2016; 16:e241-e250.
13. Ibrahim KY, Pierrotti LC, Freire MP, Gutierrez PP, Duarte Ldo P, Bellesso M, Pereira J, de Alencar Fischer Chamone D, Abdala E. Health care-associated infections in hematology-oncology patients with neutropenia: A method of surveillance. Am J Infect Control. 2013; 41:1131-1133.
14. Hangai S, Nannya Y, Kurokawa M. Role of procalcitonin and C-reactive protein for discrimination between tumor fever and infection in patients with hematological diseases. Leuk Lymphoma. 2015; 56:910-914.
15. Ogawara D, Fukuda M, Ueno S, Ohue Y, Takemoto S, Mizoguchi K, Nakatomi K, Nakamura Y, Obase Y, Honda T, Tsukamoto K, Ashizawa K, Oka M, Kohno S. Drug fever after cancer chemotherapy is most commonly observed on posttreatment days 3 and 4. Support Care Cancer. 2016; 24:615-619.

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