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ORIGINAL ARTICLE

Impact of oral hygiene on febrile neutropenia during breast cancer chemotherapy

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Abstract

Purpose Oral hygiene is crucial in the management of oral and febrile complications during chemotherapy for cancer. This study aimed to investigate the impact of oral hygiene on the incidence of febrile neutropenia (FN) throughout the course of chemotherapy for breast cancer.

Methods A total of 137 patients with breast cancer who underwent four cycles of adjuvant chemotherapy with docetaxel and cyclophosphamide (TC) combination therapy or docetaxel alone were assessed for oral hygiene by quantifying the number of oral bacteria they harbored. These patients received professional oral health care (POHC). Eighteen patients underwent primary prophylaxis with granulocyte colony-stimulating factors. The relationship between oral bacteria count and FN incidence was retrospectively assessed.

Results The FN incidence rate was 47.4% throughout all treatment cycles (32.8%, 13.5%, 14.3%, and 14.4% in cycles 1, 2, 3, and 4, respectively). The oral bacteria count decreased with each treatment cycle (cycle 1: 9.10×10^6 colony-forming units (CFU)/mL, cycle 2: 5.89×10^6 CFU/mL, cycle 3: 4.61×10^6 CFU/mL, cycle 4: 5.85×10^6 CFU/mL, $P=0.004$). Among 281 treatment cycles, FN occurred in 63 (22.4%). In the treatment cycle-based analysis, high oral bacteria count was an independent risk factor for FN.

Conclusion FN incidence decreased with each treatment cycle and was associated with changes in oral bacteria counts. The oral bacterial count was one of risk factors for FN development in breast cancer.

Keywords Breast cancer · Chemotherapy · Febrile neutropenia · Oral hygiene · Oral bacteria count

Introduction

Febrile neutropenia (FN) is defined as a febrile event during the myelosuppressive period due to chemotherapy, causing hospitalization, mortality, chemotherapy dose reduction or delay, and high medical costs [1]. The incidence of FN depends on the chemotherapy regimens, which are classified as low- (< 10%), intermediate- (10–20%), or high- (> 20%) risk for FN [2]. For example, docetaxel, a common perioperative chemotherapy for breast cancer, is an intermediate risk factor of FN. Meanwhile, docetaxel and cyclophosphamide (TC) combination chemotherapy is classified as a high-risk factor for FN [3]. Although infections during myelosuppressive chemotherapy are common, the exact cause of infection is difficult to establish, and the pathogen is isolated in < 30% of cases [4].

The oral cavity is the primary gateway to the human body. Microorganisms may translocate from the oral cavity into the systemic bloodstream via an ulcerated epithelium [5]. Additionally, previous studies have reported that oral mucositis induces febrile complications owing to the systemic spread of microorganisms [6–8]. Another study reported that 5% of the focus of infection during chemotherapy was derived from the oral cavity and teeth in patients with solid tumors

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and lymphomas, including breast cancer [9]. Professional oral health care (POHC) has been reported to reduce the incidence of oral mucositis and FN by improving overall oral hygiene during hematopoietic stem cell transplantation [10]. POHC may also be effective in preventing the onset of FN in patients receiving chemotherapy.

The number of bacteria in the oral cavity is an indicator of oral hygiene. Oral bacteria counts have been reported to be reduced by POHC and can be used to objectively assess the risk of aspiration pneumonia in elderly patients [11]. However, the relationship between FN development and oral bacteria counts in cancer patients remains unknown. This study investigated the effect of oral hygiene on the incidence of FN in patients with breast cancer who received adjuvant chemotherapy.

Patients and methods

Patients

Among patients with breast cancer who received TC (docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2, every three weeks for four cycles) or docetaxel (75 mg/m^2, every three weeks for four cycles) between January 2017 and March 2020 at Hiroshima University Hospital, those whose oral bacteria counts were assessed were retrospectively reviewed. Additionally, trastuzumab (initial dose of 8 mg/kg, followed by 6 mg/kg after cycle 2) was administered intravenously to patients with human epidermal growth factor receptor 2 (HER2)-positive disease. Anthracycline-based regimens were excluded from the study due to their use being followed by taxanes. Because oral bacteria counts were assessed in only half of all treatment cycles, FN risk was evaluated on a treatment cycle-basis as well as on a patient-basis to accurately assess the impact of real-time oral hygiene.

Definition of FN

FN was diagnosed when the patient developed a fever (axillary temperature > 37.5 °C) and had grade 3–4 neutropenia ($< 1.0 \times 10^9$ neutrophils/L) or fever during the neutropenic period (days 5–14) [12].

Evaluation and management of oral hygiene

The number of oral bacteria was measured using a rapid oral bacteria quantification system (Panasonic Healthcare Co. Ltd., Osaka, Japan) based on the dielectrophoretic impedance measurement method at arbitrary treatment cycles. A sterilized cotton swab was swiped on the tongue dorsum three times and then placed in water in the bacteria detection apparatus for counting. The estimated number of bacteria was recorded for the analysis. Bacterial count of ≥ 10 million colony-forming units (CFU)/mL was assigned to high oral bacterial level, and < 10 million CFU/mL was considered low.

POHC consisted of professional teeth cleaning, tongue cleaning with a sponge brush, supragingival scaling, and self-care instructions, including azulene gargling for preventing xerostomia. POHC was provided on each treatment day by dentists and dental hygienists, and the self-care compliance was monitored. Oral bacteria were counted throughout arbitrary treatment cycles.

Statistics

The summarized data are presented as numbers and percentages unless otherwise stated. Frequencies were compared using Fisher's exact test for categorical variables. Logistic regression analysis was used to identify the predictors of FN. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) [13].

Results

A total of 137 patients were included in this study. The patient characteristics are shown in Table 1. The median age was 50 years, and 20 patients (16.1%) were over 65 years. TC chemotherapy was administered to 74 patients (54.0%), and docetaxel alone was administered to 63 (46.0%). Additionally, 36 patients (26.3%) had HER2-positive disease. Moreover, 18 patients (13.1%) received primary prophylaxis with granulocyte colony-stimulating factors (G-CSF). Oral bacteria counts were measured 281 times (median value: 5.89×10^6 CFU/mL) and 54 cases (39.4%) displayed high oral bacteria levels. Figure 1 shows the changes in oral bacteria counts during chemotherapy. Oral bacterial count before the first, second, third, and fourth chemotherapy cycle was 9.10×10^6 CFU/mL, 5.89×10^6 CFU/mL, 4.61×10^6 CFU/mL, and 5.85×10^6 CFU/mL, respectively. Oral bacterial count decreased with each treatment cycle ($P = 0.004$).

Patient-based assessment

FN occurred in 65 patients (47.4%) throughout all treatment cycles. Furthermore, 32.8%, 13.5%, 14.3%, and 14.4% of patients in cycles 1, 2, 3, and 4 experienced FN, respectively. The frequency of FN incidence was 42.2% in patients with low oral bacteria levels and 55.6% in patients with high oral bacteria levels ($P = 0.161$). Primary

Table 1 Patients' characteristics

Characteristics	Number (%)
Age (y), median (range)	50 (27–73)
Histology	
Invasive ductal carcinoma	126 (92.0)
Others	11 (8.0)
Stage	
I	54 (39.4)
II	58 (42.3)
III	23 (16.8)
Locoregional recurrence	2 (1.5)
Estrogen receptor positive	111 (81.0)
HER2 positive	36 (26.3)
Chemotherapy	
TC	74 (54.0)
Docetaxel	63 (46.0)
Primary prophylactic G-CSF	18 (13.1)
Oral bacterial level	
Low	83 (60.6)
High	54 (39.4)

G-CSF granulocyte colony-stimulating factor, *HER2* human epidermal growth factor receptor 2, *TC* docetaxel and cyclophosphamide

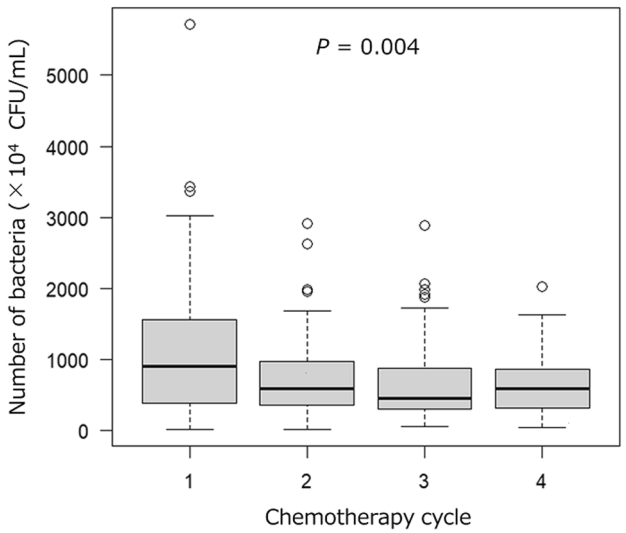

Fig. 1 Transition of oral bacterial counts during chemotherapy. CFU, colony-forming unit

prophylaxis with G-CSF tended to reduce FN incidence compared with absence of prophylaxis with G-CSF (27.8% vs. 50.4%; $P = 0.082$). Oral mucositis occurred in 71 patients (51.8%), and severe oral mucositis in 3 patients (2.2%). Oral mucositis occurrence was not related to the oral bacterial level or FN occurrence.

Treatment cycle-based assessment

A total of 548 cycles of chemotherapy were administered, and the number of oral bacteria was evaluated throughout 281 cycles. FN incidence rate was assessed according to the number of treatment cycles to reflect the oral bacteria level per cycle. FN was found to have occurred in 63 cycles (22.4%). Prophylaxis with G-CSF, including secondary prophylaxis, was performed in 24.9% of cycles (20.2% of patients < 65 and 47.9% of those ≥ 65 years of age) and numerically reduced FN development (25.1% vs. 14.3%, $P = 0.069$). Moreover, high oral bacteria levels had a significantly higher correlation with FN than low levels (37.1% vs. 17.5%, $P = 0.001$) (Table 2). In multivariate analysis, younger age and high bacteria levels were independent risk factors of FN (Table 3).

Discussion

In this study, we evaluated the impact of oral hygiene on FN incidence in patients with breast cancer who received TC or docetaxel chemotherapy. Our findings show that the oral bacteria count was related to FN development.

The mouth houses a diverse microbial community of over 700 species of bacteria that colonize the hard surfaces of teeth and soft tissues as biofilms [14]. Myelosuppressive chemotherapy reduces the salivary flow and alters the oral microbiome [15, 16], which could increase the incidence and severity of complications, including oral mucositis, oral mucosal infections, and dental caries [17, 18]. Oral mucositis is an inflammatory condition of the oral mucosa on the

Table 2 Frequency of febrile neutropenia incidence on treatment cycle-based analysis

	Number (%)	*P*
Total	63 (22.4)	
Age		0.002
< 65 y	60 (25.8)	
≥ 65 y	3 (6.2)	
Chemotherapy		0.666
TC	38 (23.5)	
Docetaxel	25 (21.0)	
Prophylactic G-CSF		0.069
No	53 (25.1)	
Yes	10 (14.3)	
Oral bacterial level		0.001
Low	37 (17.5)	
High	26 (37.1)	

G-CSF granulocyte colony-stimulating factor, *TC* docetaxel and cyclophosphamide

Table 3 Predictive factors of febrile neutropenia incidence on treatment cycle-based analysis

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age ≥ 65 y	0.19 (0.06–0.64)	0.007	0.19 (0.05–0.66)	0.009
TC chemotherapy	1.15 (0.65–2.04)	0.627	1.14 (0.62–2.10)	0.676
Prophylactic G-CSF	0.50 (0.24–1.04)	0.063	0.65 (0.30–1.43)	0.286
high oral bacterial level	2.78 (1.52–5.07)	< 0.001	2.94 (1.57–5.51)	< 0.001

CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; OR, odds ratio; TC, docetaxel and cyclophosphamide

buccal and labial surfaces, ventral surface of the tongue, floor of the mouth, and soft palate [19]. The oral cavity is the main portal of entry into the human body, as it is contiguous with the tonsils, pharynx, esophagus, eustachian tube, middle ear, trachea, lungs, nasal passages, and sinuses. Microorganisms from the oral cavity may enter the systemic circulation through compromised and/or ulcerated epithelium of the periodontal pocket [5]. Chemotherapy-induced granulocytopenia, which occurs simultaneously with oral mucositis, increases the risk of bacteremia and sepsis. Additionally, some studies have suggested that oral mucositis may induce systemic spreading of microorganisms and febrile episodes [6–8]. Obligate anaerobic bacteria have been found to account for 3.4% of bacteremia in neutropenic patients, and periodontopathogenic bacteria in the oral cavity are also assumed to be a source of infection [20]. Although a previous study reported that 5% of infections derived from the oral cavity in patients with solid tumors and lymphomas, this number may be higher considering the percentage of pathogens that cannot be identified [9].

POHC is recommended to reduce the bacterial load in the oral cavity and prevent mucositis secondary to cancer therapy [21]. High bacterial counts lead to a faster onset of mucositis and slower healing during radiotherapy in patients with head and neck caner [22]. Several previous studies have reported that the number of oral bacteria was low after POHC [11, 23]. In this study, the temporal patterns of oral bacterial counts and FN incidence were correlated, and multivariate analysis revealed that high oral bacteria levels were independent predictors of FN. Therefore, decreasing the oral bacteria count through POHC may be an effective countermeasure against febrile complications during chemotherapy. However, the causative agent of FN was not identified. In addition, the microbial diversity can change during chemotherapy [15]. To demonstrate our hypothesis, it is important to identify oral bacteria and fever-causing bacteria, and conduct a POHC comparative study.

The limitations of this study originate from its retrospective design. The frequency of FN might have been overestimated because the neutrophil count during fever was not evaluated in many cases owing to outpatient care. Although previous studies indicated that the surrogate definition of FN is reasonable, whether this definition is compatible for those that underwent prophylaxis with G-CSF is unclear [24, 25]. Moreover, FN was more common in patients younger than 65 years of age in this study; however, old age is generally a risk factor of FN. The small cohort size and high use of prophylactic G-CSF for elderly patients might have influenced these conflicting results. In addition, oral bacteria were counted throughout arbitrary treatment cycles rather than all cycles. The species of oral bacteria, the causative agent of the fever, and the activity of periodontal disease were not examined. Therefore, a prospective study with a larger cohort is warranted.

In conclusion, oral bacteria levels and FN occurrence throughout the course of chemotherapy treatment were correlated in patients with breast cancer. Our findings highlight the importance of management for reducing oral bacteria to prevent chemotherapy-induced febrile complications. The role of POHC and details of oral hygiene should be investigated in the future.

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Author contributions KS, SS, and YK contributed to the study conception and design. Clinical data collection was performed by KS, SS, YK, AE, NM, and TK. HN, TS, and HK counted the number of oral bacteria and provided professional oral health care. KS and SS analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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Data availability Not applicable.

Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the Institutional Ethics Committee for Epidemiology (No. E2016-0453).

Consent to participate Formal patient consent was not required for this retrospective study.

Consent for publication Not applicable.

Code availability Not applicable.

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