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Original Research

Dysgeusia in patients with cancer undergoing chemotherapy

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ABSTRACT

Objective: The present study aimed to identify the characteristics of dysgeusia caused by cancer chemotherapy.
Patients and methods: We investigated 181 patients with oral adverse events from cancer chemotherapy who were referred to an oral surgery clinic.
Results: Oral mucositis, dysgeusia and dry mouth were found in 62 (34.3%), 61 (33.7%) and 28 (15.5%) patients, respectively. Most dysgeusia was grade 1 (95.1%, $P < 0.001$) and was found in 20 (50.0%), 16 (43.2%) and 5 (27.8%) patients with colorectal, breast and gynecological types of cancer, respectively. Dysgeusia was identified in 14 (70.0%), 13 (76.4%) and 10 (55.6%) patients treated with oxaliplatin, paclitaxel and doxorubicin, respectively. Peripheral neuropathy (PN) was evident in 70 (38.7%) patients, and 40 patients had both PN and dysgeusia. Frequency of dysgeusia was significantly higher in patients with PN than in patients without PN ($P < 0.001$).
Conclusion: Dysgeusia tended to occur during treatment with oxaliplatin, paclitaxel and doxorubicin, and an association with PN was also suggested.

1. Introduction

Various types of cancer, including solid and hematopoietic types, have been treated with chemotherapeutic agents that also induce adverse events as defined in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0) [1]. The most common oral adverse event is oral mucositis, the clinical status and treatment strategy of which have been described in detail [2,3]. Various oral adverse events other than oral mucositis have recently been determined, probably because the application of targeted agents in addition to traditional chemotherapy agents has become more widespread [3]. One such adverse event is dysgeusia, which is included among the disorders of the nervous system and characterized by an abnormal sensual experience of the taste of foodstuffs that can be related to a decreased sense of smell. Dysgeusia is defined as an altered, noxious or unpleasant taste or loss of taste, without a change in diet in grade 1, and with a change in diet (such as oral supplements) in grade 2 (CTCAE version 5.0) [1]. Dysgeusia is not usually accompanied by visible changes such as oral mucositis, and grades 3, 4 and 5 have not been defined. Dysgeusia impairs nutritional intake due to changes in taste, and can persist long after chemotherapy is completed, resulting in a decreased quality of life [4–6]. The incidence of dysgeusia seems likely to increase in the future [4,7]. The present study assessed the frequency of oral adverse events, as well as types of cancer and chemotherapeutic agents associated with dysgeusia. An association between dysgeusia and peripheral neuropathy (PN) was also analyzed.

2. Patients and methods

2.1. Patients (Table 1)

Saitama Medical Center (SMC) is a regional central hospital with an Advanced Tertiary Medical Center and a Center for Maternal Fetal and Neonatal Medicine. Patients with various types of cancer are accepted for surgery, chemotherapy and radiotherapy. The present study included 181 patients (93 males, 88 females; male:female ratio, 1.04:1; median age, 62.2 years; range, 18–90 years) with oral adverse events resulting from cancer chemotherapy who were referred to the oral surgery clinic by other clinics within the SMC between April 1, 2016 and August 31, 2017. Terminal patients who had received cancer chemotherapy but were presently under adductive treatment were excluded, because not all causes of adverse oral symptoms in such cases

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Table 1
Types of cancer, n (%).

Cancer type	Male	Female	n (%)
Hematological	39	17	56 (30.9%)
Colorectal	28	12	40 (22.1%)
Breast	0	37	37 (20.4%)
Gynecological	0	18	18 (9.9%)
Urological	11	0	11 (6.1%)
Lung	6	2	8 (4.4%)
Pancreatic	2	1	3 (1.7%)
Gastric	2	1	3 (1.7%)
Other[a]	5	0	5 (2.8%)
Total	93	88	181 (100%)

[a] Comprising three patients with esophageal cancer and one patient each with bile duct and cerebral cancer.

could be attributed to chemotherapy. Patients who had received concomitant radiotherapy for the cancer of head and neck were also excluded.

2.2. Statistical analysis

Oral adverse events were graded according to the categories listed in the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) [1]. We assessed the prevalence of dysgeusia among various types of cancers. Chemotherapeutic agents included in regimens for > 10 patients in the subject cohort were also investigated, and associations between dysgeusia and PN were analyzed. Data were statistically analyzed using Origin pro 2016 software (Lightstone Corp., Tokyo, Japan) using chi-square tests. The level of significance for all tests was set at 5% ($P < 0.05$).

3. Results

Among the 181 patients in the study cohort, 56 (30.9%), 40 (22.1%), 37 (20.4%), 18 (9.9%), 11 (6.1%) and 8 (4.4%) had hematological, colorectal, breast, gynecological, urological and lung cancers (Table 1). The most frequent oral adverse events were mucositis, dysgeusia, dry mouth and dysesthesia in 62 (34.3%), 61 (33.7%), 28 (15.5%) and 14 (7.7%) patients, respectively. No other adverse events were encountered. Dysgeusia ($P < 0.001$), dry mouth ($P = 0.009$) and oral dysesthesia ($P < 0.001$) were significantly prevalent grade 1 events. Grade 1 dysgeusia and oral dysesthesia were significantly more prevalent than oral mucositis ($P < 0.001$ and $P = 0.02$, respectively; Table 2). Patients with dysgeusia included 28 males and 33 females (male:female ratio, 1:1.18), with a median age of 63.0 years (range, 18–82 years). Dysgeusia was found in 10 (18%), 20 (50.0%), 16 (43.2%), 5 (27.8%), 2 (18.1%), 2 (25.0%), 3 (0.0%) and 3 (100.0%) patients with hematological, colorectal, breast, gynecological, urological, lung, pancreatic and gastric types of cancer, respectively (Table 3). Ratios of dysgeusia did not significantly differ among colorectal, breast and gynecological cancers, although a relatively higher ratio was associated with colorectal cancer. The rate of dysgeusia was significantly lower among patients with hematological cancers than among patients with colorectal, breast and gynecological cancers ($p < 0.0025$; Table 3). Among those patients with chemotherapeutic agents administered to > 10 patients, dysgeusia was identified in 17 (77.2%) of 22, 10 (47.6%) of 21, 14 (70.0%) of 20, 10 (55.6%) of 18, 13 (76.4%) of 17, 3 (25.0%) of 12, 3 (27.2%) of 11, 9 (90.0%) of 10 and 3 (30.0%) of 10 patients administered bevacizumab, cyclophosphamide, oxaliplatin, doxorubicin, paclitaxel, cytarabine, prednisolone, tegafur, gimeracil, oteracil potassium (TS-1®) and vincristine, respectively (Table 4). Among the 70 (38.7%) patients with PN, 40 also had dysgeusia. The frequency of dysgeusia was higher ($P < 0.001$) among patients with PN than among those without PN (Table 5).

Table 2
Types and severity of oral adverse events, n (%).

	Grade 1	Grade 2	Grade 3	n (%)	P (1 vs. 2 + 3)
Oral mucositis	36	19	7	62 (34.3%)	0.05
Dysgeusia	58	3	–	61 (33.7%)	0.001
Dry mouth	21	6	1	28 (15.5%)	0.009
Oral dysesthesia	13	1	0	14 (7.7%)	< 0.001

Grade 1 dysgeusia and oral dysesthesia are significantly more frequent than oral mucositis ($P < 0.001$ and $P = 0.02$, respectively).

Table 3
Ratios of dysgeusia among different types of cancer, n (%).

Type of cancer	Patients with dysgeusia, n (%) / Total n
Hematological	10 (18.0%) / 56[†]
Colorectal	20 (50.0%) / 40
Breast	16 (43.2%) / 37
Gynecological	5 (27.8%) / 18
Urological	2 (18.1%) / 11
Lung	2 (25.0%) / 8
Pancreatic	0 (0.0%) / 3
Gastric	3 (100.0%) / 3
Other[*]	0 (0.0%) / 5

[*] Comprising three patients with esophageal cancer and one patient each with bile duct and cerebral cancers.

[†] Rate of dysgeusia is significantly lower among patients with hematological cancers than among patients with colorectal, breast and gynecological cancers ($p < 0.0025$).

Table 4
Ratios of dysgeusia among chemotherapeutic agents, n (%)[a].

Agent	Patients with dysgeusia, n (%) / Total n
Bevacizumab	17 (77.2%) / 22
Cyclophosphamide	10 (47.6%) / 21
Oxaliplatin	14 (70.0%) / 20
Doxorubicin	10 (55.6%) / 18
Paclitaxel	13 (76.4%) / 17
Cytarabine	3 (25.0%) / 12
Prednisolone	3 (27.2%) / 11
Tegafur, gimeracil, oteracil potassium (TS-1®)	9 (90.0%) / 10
Vincristine	3 (30.0%) / 10

[a] Included in regimens that caused dysgeusia in > 10 patients.

Table 5
Comparison between dysgeusia and peripheral neuropathy.

Dysgeusia[a]	61 (33.7%)
With PN	40
Without PN	21
PN[a]	70 (38.7%)
With dysgeusia	40
Without dysgeusia	30

[a] Rate of dysgeusia is significantly higher among patients with peripheral neuropathy (PN) than among patients without PN ($P < 0.001$). Data are shown as n or n (%).

4. Discussion

The present study found that the most frequent oral adverse events associated with cancers and cancer treatments were mucositis, followed by dysgeusia and dry mouth. The most common oral adverse event to date requiring special care has been oral mucositis, and its clinical appearance and treatment strategy have been described in detail [2,3].

In contrast, dysgeusia has received less focus, yet the prevalence has increased. Therefore, not only mucositis, but also other oral events such as dysgeusia that are associated with cancer chemotherapy should be adequately explained to patients [8].

Taste perception starts when tastants reach taste receptor cells in taste buds and taste signals are transmitted to sensory neurons [9]. Taste from the anterior two-thirds of the tongue is transmitted by the chorda tympani branch of the facial nerve, and the lingual branch of the trigeminal nerve. The posterior third of the tongue, oropharynx, and esophagus are innervated by the glossopharyngeal and vagus nerves [9]. Disruption of taste buds and associated nerves therefore causes dysgeusia.

The main symptom of dysgeusia is a decrease or alteration in or loss of taste. Types of changes in taste are highly variable, but a loss of saltiness perception has been described as the most common, followed by losses of umami and sweetness [4]. Dysgeusia develops within 1 to 15 weeks after initiating chemotherapy [10]. Taste sensation improves in most patients after chemotherapy is completed, but dysgeusia can persist for long periods thereafter [11]. Persistent dysgeusia results in weight loss that requires essential nutritional support. Dysgeusia includes not only changes in taste, but also the acquisition of a metallic, chemical or bitter sensation, resulting from taste bud impairments that have been attributed to the secretion of chemotherapeutic drugs into saliva or diffusion from capillaries [12].

Compared with oral mucositis, which can reach grade ≥ 3, dysgeusia, dry mouth and oral dysesthesia are usually grade 1 events. This could explain the emphasis on mucositis, compared with other oral adverse events.

The present study found that dysgeusia was more frequently associated with colorectal, breast and gynecological types of cancer, which should be considered along with the types of agents administered to treat the cancer. The occurrence of dysgeusia was relatively high (˜50% of treated patients) when regimens included bevacizumab, paclitaxel, oxaliplatin, doxorubicin, cyclophosphamide and TS-1®. No pharmacological and clinical reports have suggested that dysgeusia occurs under monotherapy with either bevacizumab or cyclophosphamide [2]. Conversely, paclitaxel, oxaliplatin and doxorubicin are neurotoxins [13,14] that are commonly administered to treat colorectal, breast and gynecological cancers, as well as malignant lymphomas [15–17]. Notably, dysgeusia frequently occurs when regimens include these three agents [7,18]. Dysgeusia developed in 90% of patients with regimens including TS-1® However, few reports have described an association between dysgeusia and regimens including TS-1®, and the occurrence of dysgeusia described in these reports was not high [19]. The present study found that dysgeusia developed in all except one patient while under chemotherapy with combined oxaliplatin and TS-1®. The association with dysgeusia seems much closer for oxaliplatin than for TS-1®. Our results suggested that dysgeusia tends to occur in colorectal, breast and gynecological cancers that are specifically treated with paclitaxel, oxaliplatin or doxorubicin. In addition, all three patients with gastric cancer developed dysgeusia. However, more information is needed before further discussion can proceed.

We investigated an association between dysgeusia and PN, characterized by inflammation, or the degeneration of peripheral motor or sensory nerves (CTCAE version 5.0) [1]. The symptoms of PN include numbness, tingling, paresthesia and dysesthesia induced by touch, warm or cool temperatures, as well as impaired vibration and altered touch sensations [20]. Platinum-based agents (oxaliplatin and cisplatin), vinca alkaloids (vincristine and vinblastine), epothilones (ixabepilone), diterpenes (taxanes; paclitaxel, docetaxel), antimetabolites (cytarabine), proteasome inhibitors (bortezomid) and immunomodulatory drugs (thalidomide) can induce PN [13], and the mechanism of dysgeusia is mainly understood to involve neurological damage [21]. An association between dysgeusia and PN has been identified [22]. The present study found a significantly higher frequency of dysgeusia among patients with PN than among patients without PN, and that oxaliplatin and paclitaxel were frequent components of regimens causing dysgeusia. These results suggested that the occurrence of dysgeusia is closely associated with PN.

A standard treatment that can decisively improve or prevent dysgeusia has not yet been determined [22,23]. Zinc supplementation is common, but its effectiveness reportedly varies [12]. Drugs to treat PN include analgesic, anticonvulsant and antidepressant medications, but the effects on PN are limited and those for dysgeusia have not been verified [13]. Oral hygiene has been described as important for improving dysgeusia, as its effect on oral mucositis has been established [2,3]. Essentially, oral mucositis damages epithelial cells, including taste receptor cells, and secondary infection by oral microorganisms further worsens mucositis, while a dry mouth hampers food particle solubilization, resulting in decreased presentation of tastants to taste receptors [12]. Maintaining a clean, moist oral cavity might help to prevent taste alterations.

The major limitation of this study was the small number of investigated patients and the numbers of those administered drugs specific to each type of cancer. The influence of combination chemotherapeutic regimens, in which interactions among agents might increase or decrease the potential for developing dysgeusia, were not adequately considered. Further large-scale studies are needed.

5. Conclusions

Dysgeusia is not a life-threating adverse event and most instances are grade 1 events. However, effective methods to improve dysgeusia induced by chemotherapy remain unknown. Dysgeusia might be associated with current chemotherapeutic regimens and PN, as it tended to develop in patients while under paclitaxel, oxaliplatin and doxorubicin regimens for treating specific cancers.

Ethical approval

The Ethics Review Board at Saitama Medical University approved the protocol of the study, which proceeded in accordance with the Declaration of Helsinki.

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