Cancer Chemotherapy-Induced Oral Adverse Events: Oral Dysesthesia and Toothache - A Retrospective Study

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Abstract

Introduction: Due to the development of newly developed anticancer drugs, oral dysesthesia and toothache other than conventional oral mucositis, dry mouth, and dysgeusia are increasing among oral adverse events. The objective of this study was to assess the characteristics of chemotherapy-induced oral dysesthesia and toothache. **Materials and Methods**: Subjects were patients referred to the oral surgery clinic for oral adverse events related to cancer chemotherapy and with an observation period of more than 1 month after the last course of chemotherapy. Oral adverse events were divided according to the categories of the National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0. Statistical comparison was made using the binomial test. **Results**: A total of 180 patients were referred to the oral surgery clinic. Oral dysesthesia and/or toothache was found in 15 cases, which included 13 with oral dysesthesia, 4 with toothache, and 2 with both oral dysesthesia and toothache. Of these 15 cases, 13 had concomitant occurrence of peripheral neuropathy (PN) (86.7%, $P = 0.0037$) and 12 cases had dysgeusia (80.0%, $P = 0.0176$). Symptoms of oral dysesthesia and/or toothache continued after chemotherapy in 10 of 15 cases with the continuation of accompanied PN (66.7%) and/or dysgeusia and persisted for more than 6 months in 5 cases (33.3%). **Discussion:** Although oral dysesthesia and toothache are low-grade chemotherapy-induced adverse events, it is suggested that they may be nervous system disorders rather than gastrointestinal disorders. Clinicians should understand that they potentially persist for a long period after the end of chemotherapy.

Keywords: Adverse events, chemotherapy, oral dysesthesia, toothache

Introduction

The number of cancer patients has increased in recent years, and chemotherapeutic agents have contributed to the treatment of various types of cancer, including both solid and hematopoietic types.[1] At the same time, adverse events from chemotherapy have also been increasing.[2] The adverse events are various and are described precisely in the list of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), v5.0.[3] Among these, various oral adverse events can be found in the categories of gastrointestinal disorders and nervous system disorders. The common oral adverse events include oral mucositis, dry mouth, and dysgeusia.[4] Patients suffering from mucosal discomfort without mucosal change and tooth hypersensitivity are more frequently seen at present, probably because of newly developed chemotherapeutic agents.[5] These mucosal and tooth complications are divided into oral dysesthesia and toothache, respectively, in the CTCAE v5.0.[3] Oral dysesthesia and toothache, which are classified as gastrointestinal disorders, are relatively low-grade adverse events, but it is unclear whether it is appropriate to classify them as gastrointestinal disorders even though they include perceptual complications. Among oral adverse events, the clinical characteristics and treatment strategies for oral mucositis and dry mouth have

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been well described.[5] However, studies into oral dysesthesia and toothache are rare.[4-6] As chemotherapy-induced oral dysesthesia and toothache are expected to become more common with the development of biological targeted therapies and immune checkpoint inhibitors, it is worthwhile to improve our understanding of oral dysesthesia and toothache.[4,5] The objective of this study was to assess the characteristics of cancer chemotherapy-induced oral dysesthesia and toothache and describe the association between nervous system disorders and oral dysesthesia and toothache.

Materials and Methods

The Ethics Review Board at the University approved the protocol of the study (approval number: 2018-1878), which proceeded in accordance with the Declaration of Helsinki. Patients referred to the oral and maxillofacial surgery clinic for oral adverse events related to cancer chemotherapy from other clinics from April 1, 2016 to September 30, 2018 were searched. Data on these patients were obtained from their clinical records, and they were analyzed retrospectively. In these, patients who had an observation period of more than 1 month after the last course of chemotherapy were included as subjects in the study. Patients were excluded if they did not have complete medical records. In addition, patients receiving palliative care were excluded because these patients had various oral complications not related to chemotherapy, and patients with head and neck cancer were excluded because tumour progress and/or radiotherapy cause oral complications. Oral adverse events in patients were divided according to the categories of CTCAE v5.0.[3] As some oral events described in CTCAE v5.0 are broad and difficult to classify clinically into one event, in this study, "oral pain" and "oral dysesthesia," both of which are defined as events with no change in the mucosa, were classified under the term "oral dysesthesia". In addition, bisphosphonate and denosumab are used to treat cancer, but this "oral dysesthesia" does not include early symptoms of medication-related osteonecrosis of the jaw. As there are no eligible criteria that describe hypersensitivity and dysesthesia of teeth except for "toothache", "toothache" was used as the term for hypersensitivity and dysesthesia of teeth. In addition, this "toothache" is not caused by an odontogenic cause such as dental caries, impacted teeth, and any other pathologies.

In this study, patients with oral dysesthesia and/or toothache were subsequently compiled and their chemotherapy and adverse events data were analyzed. Data were statistically analyzed by the binomial test using Origin Pro 2016 software (Lightstone Corp., Tokyo, Japan). The level of significance for all tests was set at 5% ($P < 0.05$).

Results

A total of 188 patients were referred to the oral surgery clinic. Two patients were excluded from this study due to the absence of precise medical records, and six patients were excluded because the observation period was shorter than 1 month after the last course of chemotherapy. As a result, 180 patients were enrolled in this study. Among these, there were 15 cases of oral dysesthesia and/or toothache, in which oral dysesthesia was found in 13 cases and toothache was found in 4 cases. Two cases showed both oral dysesthesia and toothache. The details of patients with oral dysesthesia and/or toothache are shown in Table 1. There were 8 men and 7 women, whose ages ranged from 36 to 80 (60.3 ± 13.9) years. Thirteen cases had concomitant peripheral neuropathy (PN) (86.7%, $P = 0.0037$) and 12 cases had dysgeusia (80.0%, $P = 0.0176$). Drugs that are known to cause PN were used in 12 cases; 4 used taxanes (2 each of docetaxel and paclitaxel), 4 used oxaliplatin, 3 used vincristine, and 1 used cytarabine. The most common symptom of oral dysesthesia was tingling of the tongue (8/13) (61.5%, $P = 0.5000$) and all 4 cases of toothache showed hypersensitivity to cold stimulation (100.0%). The onset of oral dysesthesia and/or toothache was at the same time of PN in 4 cases (30.8%) and later than that of PN in 9 cases (69.2%). Symptoms of oral dysesthesia and/or toothache continued after chemotherapy in 10 of 15 cases with the continuation of accompanying PN and/or dysgeusia (66.7%) ($P = 0.1509$) and persisted for more than 6 months in 5 cases (33.3%).

Discussion

In this study, the characteristics of cancer chemotherapy-induced oral dysesthesia and toothache were described, and the association between nervous system disorders and oral dysesthesia and toothache was discussed.

Adverse events, including oral events, can vary based on the chemotherapy regimen. The most common oral adverse events are oral mucositis, dysgeusia, and dry mouth,[4,7,8] while the occurrence of oral dysesthesia and toothache is somewhat less common. A recent study noted that 12% of patients who were treated with vascular endothelial growth factor receptor-directed multitargeted tyrosine kinase inhibitor therapies had oral dysesthesia.[4] In this study, oral dysesthesia and toothache were found in 7.2% (13/181) and 2.2% (4/181), respectively.[4]

Oral dysesthesia is a gastrointestinal disorder and is characterized by a burning or tingling sensation on the lips, tongue, or the entire mouth (CTCAE v5.0).[3] In CTCAE v5.0, oral pain, which is defined as a disorder characterized by a sensation of marked discomfort in the mouth, tongue, or lips, presents as a complication of the oral mucosa, similarly to oral dysesthesia. It is difficult to distinguish these two events clinically; thus, in this study, the term "oral dysesthesia" was used to describe mucosal discomfort without mucosal change. Toothache is also a gastrointestinal disorder and is characterized by a sensation of marked discomfort in the tooth (CTCAE v5.0). There are no criteria that describe tooth hypersensitivity and discomfort other than "toothache" in CTCAE v5.0. The precise study of oral dysesthesia and toothache is rare.[4-6]

Table 1: Characteristics of patients with oral dysesthesia and/or toothache

Case	Sex	Age (years)	Cancer diagnosis	Regimen	Adverse events and postchemotherapeutic continuation						Details of oral dysesthesia and/or toothache	
					Nervous system disorders		Gastrointestinal disorders					
					Peripheral neuropathy	Dysgeusia	Mucositis oral	Dry mouth	Oral dysesthesia	Toothache	Symptoms	Time of onset
1	Female	68	Peritoneal cancer	DTX, Bev	G3 <3 m	G1-	G1-	-	G1 <3 m	-	Tingling of the apex of the tongue	After PN
2	Male	66	Malignant lymphoma	VCR, DXR, CPA, PSL, rituximab	G2 >6 m	G2 >6 m	-	-	G1 >6 m	G1 >6 m	Tingling of the apex of the tongue hypersensitivity of teeth (cold)	After PN
3	Male	54	Malignant lymphoma	Bendamustine, rituximab	G1 >6 m	G1 >6 m	G3-	G1 >6 m	G1 >6 m	-	Tingling of the apex of the tongue hypesthesia of the oral mucosa	Same with PN
4	Female	44	Pancreatic cancer	L-OHP, 5-FU, CPT-11	G1 >3 m	G1 >3 m	G2-	G2--	G1 >3 m	-	Hypesthesia of the entire oral mucosa	After PN
5	Male	70	Rectal cancer	L-OHP, TS-1, Bev	G1 >6 m	G1	-	-	G1-	-	Tingling of the apex of the tongue	After PN
6	Female	62	Ovarian cancer	DTX, CBDCA, Bev	G2 >6 m	G2 >6 m	-	G2-	G1-	-	Hypesthesia of the apex of the tongue	Same with PN
7	Male	80	Colorectal cancer	L-OHP, 5-FU	G1 >6 m	G1 >6 m	G2	-	-	G1-	Hypersensitivity of teeth (cold)	After PN
8	Male	44	Malignant lymphoma	VCR, DXR, CPA, PSL	-	G1 >12 m	-	-	-	G1 >12 m	Hypersensitivity of teeth (cold)	/
9	Female	57	Colorectal cancer	Cetuximab, CPT-11, 5-FU	G1 DM >3 m	-	-	-	G1 >3 m	-	Tingling of the apex of the tongue	Same with PN
10	Male	77	Gastric cancer	PTX	G1 >1 m	G1 >1 m	G2	G2	G1 >1 m	-	Hyperesthesia of entire oral mucosa (hot)	After PN
11	Male	76	Colorectal cancer	L-OHP, Bev, Capecitabine	G1 >6 m	-	G2-	G1 >6 m	G1 >6 m	-	Hyperesthesia of entire oral mucosa (hot)	After PN
12	Male	59	Colorectal cancer	5-FU, CPT-11, Bev	G2 >6 m	G1 >6 m	G3-	-	G1 >6 m	-	Tingling of the tongue	Same with PN
13	Female	48	Gastric cancer	PTX	G1 >3 m	G1-	G2-	-	G1-	-	Tingling of the apex of the tongue	After PN
14	Female	36	Leukemia	AraC	-	-	G3-	-	G1-	G1-	Tingling of the apex of the tongue hypersensitivity of teeth (cold)	/
15	Female	70	Malignant lymphoma	VCR, DXR, CPA, PSL, rituximab	G1 >1 m	G1 >1 m	G1-	G2 >1 m	G1 >1 m	-	Tingling of the lips	After PN

AraC=Cytarabine; CBDCA=Carboplatin; CPA=Cyclophosphamide; CPT-11=Irinotecan; DTX=Docetaxel; DXR=Doxorubicin; 5-FU=Fluorouracil; G=Grade of National Cancer Institute Common Terminology Criteria for Adverse Events (v5.0) (G1- mild, G2- moderate, and G3-severe); L-OHP=Oxaliplatin; PN=Peripheral neuropathy; PSL=Prednisolone, PTX – Paclitaxel; TS-1=Tegafur/Gimeracil/Oteracil; VCR=Vincristine; m=Months

Recently, an association between PN and oral dysesthesia was suggested.[4,9] PN is classified as a nervous system disorder in CTCAE v5.0 and is a common adverse event of chemotherapy.[3] PN includes both motor and sensory neuropathy and can be characterized by inflammation or degeneration of peripheral motor or sensory nerves (CTCAE v5.0). The pathophysiological processes of PN are multifactorial and involve oxidative stress, apoptotic mechanisms, altered calcium homeostasis, axon degeneration, and membrane remodeling, as well as immune processes and neuroinflammation.[10-12] PN is characterized by predominantly sensory axonal PN with longer axons affected first, such as in the feet and hands.[13,14] The histopathological changes associated with PN commonly involve large myelinated fibers,[15] and the symptoms include numbness, tingling, paresthesia, and dysesthesia induced by touch, warm or cool temperatures, impaired vibration, and altered touch sensations.[16] Platinum-based agents (oxaliplatin and cisplatin), vinca alkaloids (vincristine and vinblastine), epothilones (ixabepilone), diterpenes (taxanes; paclitaxel and docetaxel), antimetabolites (cytarabine), proteasome inhibitors (bortezomib), and immunomodulatory drugs (thalidomide) are known to induce PN.[12]

In this study, 13 of 15 oral dysesthesia and/or toothache cases had concomitant PN (86.7%, $P = 0.0037$), and there were various oral dysesthesia and/or toothache-inducing drugs, but 12 of the 15 cases used oxaliplatin, paclitaxel, docetaxel, vincristine or cytarabine, which are known to cause PN. In addition, 12 of the 15 oral dysesthesia and/or toothache cases concomitantly developed dysgeusia (80.0%, $P = 0.0176$), which is a nervous system disorder. These results suggest that oral dysesthesia and/or toothache is closely associated with PN and dysgeusia, although oral dysesthesia and toothache are considered to be gastrointestinal disorders, not nervous system disorders, in CTCAE v5.0.

In this study, the most frequently affected site for oral dysesthesia was the tongue, particularly the apex of the tongue, irrespective of the drugs administered. The oral mucosa appeared to be largely intact, except in cases with mucositis. The major symptom of oral dysesthesia in almost all cases was tingling of the tongue (8/13) (61.5%), not severe pain, and this finding was consistent with previous reports.[6] All toothache cases showed hypersensitivity to cold stimulation on vital teeth. In all cases, the affected teeth were not random, but were concentrated in one block; for example, the left side of the maxilla.

PN is a dose-dependent adverse effect, and so may be oral dysesthesia and/or toothache. In this study, there were no cases in which oral dysesthesia and/or toothache occurred before PN. The occurrence of oral dysesthesia and/or toothache may require greater dose accumulation than PN. In 10 of 15 cases (66.7%), symptoms of oral dysesthesia and/or toothache continued after the end of chemotherapy with the continuation of accompanied PN and/or dysgeusia, and 5 cases (33.3%) persisted for more than 6 months. Oral dysesthesia and/or toothache is a low-grade adverse event, but may also be a long-term persistent event.

Burning mouth syndrome (BMS) is a lesion that shows similar symptoms as chemotherapy-induced oral dysesthesia. BMS is defined as a chronic condition characterized by a burning sensation in the oral mucosa for which no cause can be found. The etiology of BMS and pathogenesis is uncertain, but both psychogenic factors and peripheral and central neuropathies appear to be involved.[17] BMS frequently occurs in the tongue, and occurrence in other sites is rare.[18] In contrast to chemotherapy-induced oral dysesthesia, it is rare that BMS accompanies other chronic neuropathic pain disorders.[17] It is explained that the reason why BMS is frequent in the tongue is that the lingual mucosa, as compared to other sites in the oral mucosa, exhibits a decreased number of small diameter nerve fibers and that the remaining small-diameter nerve fibers show upregulation of the transient receptor potential subfamily member V 1 (TRPV1) ion channel, and upregulation of P2 × 3 receptors and nerve growth factor.[17,19] The tongue mucosa seems to be a neurologically sensitive site. The causes of oral dysesthesia and BMS are different, but the mechanical process of chemotherapy-induced oral dysesthesia and BMS may be closely associated.

In clinical settings, as oral dysesthesia is a low-grade adverse event (≤grade 3), almost all cases of oral dysesthesia have been removed from the object of treatment. As a practical matter, however, there have been no established regimens to prevent or reduce oral dysesthesia. It is recommended to avoid irritating foods.[5] In cases of PN, analgesic medications including anticonvulsants (pregabalin, gabapentin, carbamazepine, oxcarbazepine, lamotrigine, and topiramate) and antidepressants (amitriptyline, nortriptyline, venlafaxine, and duloxetine) are used. However, their effects are limited.[12] Accordingly, current treatment strategies for severe PN are predominantly based on dose reduction, changes to less effective chemotherapeutic agents, or even cessation of therapy.[12,20] In this study, cases with persistent PN were given one or more of these analgesic medications, and in severe PN cases, dose reduction was performed. There have been some reports of analgesic medications for PN being used for oral dysesthesia, but their effectiveness has not been verified.[5] In this study, patients with PN reported that concomitant oral complications were improved to some degree. Local application of capsaicin, which can bind to TRPV1 ion channels, is reported to be effective for the treatment of BMS, but there has been no study into capsaicin being used for chemotherapy-induced oral dysesthesia.[21]

Good oral hygiene is a basic and important means of preventing and reducing the severity of oral mucositis. It has also been noted that oral hygiene is an essential treatment for other oral adverse events, such as oral dysesthesia and dysgeusia,[5] probably because it prevents local secondary inflammation and irritation.

Toothache can be reduced by dental treatments such as application of antihypersensitive agents and/or covering of the tooth surface with dental cement.[22] However, the effects are limited when the sensitive area is large. Splints that cover the tooth surface may be effective for hypersensitivity in multiple teeth. In addition, the differentiation of chemotherapy-induced toothache from dental caries and tooth hypersensitivity is important.[23,24]

Some limitations of the present study should be considered. First, the data were collected retrospectively. Second, the relatively small number of participants means that the more accurate statistical analysis was difficult, and additional studies with larger cohorts were therefore required.

Conclusion

Although oral dysesthesia and toothache are low-grade chemotherapy-induced adverse events, it is suggested that they may be nervous system disorders rather than gastrointestinal disorders. Clinicians should understand that they potentially persist without effective treatment for a long period after the end of chemotherapy.

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Conflicts of interest

There are no conflicts of interest.

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