Journal of Dental Sciences (2021) 16, 375–379

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jds.com

Original Article

Questionnaire survey of angiogenesis inhibitor-related oral complications based on a nation-wide study in Japan

Shin-ichi Yamada [a,b*], Hiroshi Kurita [a,b], Akira Tanaka [b,c], Masaru Miyata [b,d], Yoshinari Morimoto [b,e], Akira Yamaguchi [b,f], Souichi Yanamoto [b,g], Hiromasa Yoshikawa [b,h], Yutaka Imai [i,j]

[a] *Department of Dentistry and Oral Surgery, Shinshu University School of Medicine, Matsumoto, Japan*
[b] *Committee for Survey, Planning, Promotion of Guidelines, and Projects, Japanese Society of Dentistry for Medically Compromised Patient, Kita-ku, Japan*
[c] *Department of Oral and Maxillofacial Surgery, School of Life Dentistry at Niigata, The Nippon Dental University, Niigata, Japan*
[d] *Department of Dentistry and Oral Surgery, Ishikawa Prefectural Central Hospital, Kanazawa, Japan*
[e] *Department of Critical Care Medicine and Dentistry, Graduate School of Dentistry, Kanagawa Dental University, Yokosuka, Japan*
[f] *Department of Oral and Maxillofacial Surgery, Niigata Hospital, The Nippon Dental University, Niigata, Japan*
[g] *Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*
[h] *Department of Dentistry and Oral Surgery, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan*
[i] *Department of Oral and Maxillofacial Surgery, Dokkyo Medical University School of Medicine, Mibu, Japan*
[j] *Japanese Society of Dentistry for Medically Compromised Patient, Kita-ku, Japan*

Received 9 January 2020; Final revision received 30 January 2020
Available online 15 March 2020

KEYWORDS
Angiogenesis inhibitor;
VEGF;
Oral complication;
Osteonecrosis of the

Abstract *Background/purpose:* The prevalence of oral adverse events and dental treatments related complications during the molecular targeted drugs therapy remains unclear. The purpose of this study was to investigate the contents of dental treatment-related complications in Japanese patients during molecular targeted therapy.
Materials and methods: The nation-wide survey of dental treatment related complications was performed by the Japanese Society of Dentistry for Medically Compromised Patient as retrospective cohort study.

* Corresponding author. Department of Dentistry and Oral Surgery, Shinshu University School of Medicine, 3-1-1, Asahi, Matsumoto, 390-8621, Japan. Fax:+81 0 263 37 2676.
E-mail address: yshinshin@shinshu-u.ac.jp (S.-i. Yamada).

https://doi.org/10.1016/j.jds.2020.01.004

jaw;
Hemorrhage

Results: Among 212 dentists, 87.3% recognized the possibility of dental treatments related complications in patients with angiogenesis inhibitors. The oral adverse events including dental treatment-related complications associated with angiogenesis inhibitors were 79 cases. In patients with angiogenesis inhibitors, 73.4% of patients were administrated with bevacizumab. The average administration period of angiogenesis inhibitors was 14.0 ± 10.0 months. As the dental treatment related complications, delayed wound healing was most commonly seen in 45 patients (57.0%), followed by osteonecrosis of the jaw in 25 (31.6%). The triggered factor of complications was tooth extraction in 51 cases (96.2%).
Conclusion: The extraction of the tooth with pre-existing inflammation may be suggested as one of risk factors for angiogenesis inhibitor-related dental treatment complications.

Introduction

The oral complications related to cancer chemotherapy result in the decline of the oral function. The decline of the oral function also affect the cancer treatment and patient's quality of life. Recently, molecular targeted therapy has been developed and widely administrated in some cancer patients. Their therapeutic mechanism results from the inhibitory effects on the specific molecular receptors and intracellular signaling pathways regarding the progression of the tumor. Most frequently observed adverse events are cutaneous toxicities in the patients treated with targeted therapies.[1] However, oral toxicities induced by molecular target therapy sometimes reveal characteristic features with obvious differences from classic oral complications induced by cytotoxic chemotherapy agents with/without radiotherapy.[1]

In Japan, molecular targeted drugs, which includes low molecular compounds and antibody drug, have been widely administrated in various cancer patients. Because molecular targeted drugs for cancer treatments effect on targeting molecules in signal transduction pathways that are involved in the biological properties of cancer cells, unlike conventional anticancer drugs, no unexpected adverse events observed with generally good tolerability.[2] However, a variety of specific adverse events have been reported depending on the molecular targeted molecules.[3,4] Regarding oral adverse events, various clinical symptoms were reported such as mucositis, gingival bleeding, osteonecrosis of the jaw, and dysgeusia, etc.[1,5,6]

On the other hand, there were only some reports of the oral adverse events induced by molecular targeted drugs in Japanese cancer patients, which was based on small number of patients at single institute.[7,8] Therefore, the prevalence of oral adverse events and dental treatments related complications during the molecular targeted drugs therapy remains unclear. The purpose of this study was to investigate the contents of dental treatment-related complications in Japanese patients during molecular targeted therapy, based on the nationwide questionnaire survey focused on angiogenesis inhibitors related oral complications, which was conducted by the Japanese Society of Dentistry for Medically Compromised Patient.

Materials and methods

This study protocol was approved by the Committee on Medical Research of Shinshu University (♯4490). We published a research plan and guaranteed an opt-out opportunity on the homepage of our department.

This nation-wide survey of dental treatment related complications in patients treated with angiogenesis inhibitors was performed in March 2019 by the Committee of for Survey, Planning, Promotion of guidelines, and Projects, Japanese Society of Dentistry for Medically Compromised Patient as retrospective cohort study. Detailed information on the patients who were received dental treatments during the angiogenesis inhibitors administration was obtained by written questionnaires sent by the Japanese Society of Dentistry for Medically Compromised Patient to 1230 members of this Society in February 2019. These members belonged to the university hospitals and major municipal or private hospitals having the oral and maxillofacial surgery department. The questionnaires included dentist's recognition and experience of potential dental treatment-related complications during angiogenesis inhibitor administration, the contents of dental treatment-related complications, its triggered dental treatment, the clinical symptoms of treated tooth, concurrent use of corticosteroids and other anticancer drugs, radiographic findings, medical comorbidities such as diabetes mellitus, discontinuation of angiogenesis inhibitors during the dental treatments, and complications related to the discontinuation of angiogenesis inhibitors. Data were corrected and analyzed on above contents. Regarding the diagnostic criteria of osteonecrosis of the jaw was followed by the American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw-2014 Update.[9]

Results

Among the 1230 members of the Japanese Society of Dentistry for Medically Compromised Patient, 212 dentists (17.2%) responded. Among 212 dentists, 185 (87.3%) recognizes the possibility of dental treatment-related complications in patients with angiogenesis inhibitors. One

hundred and thirteen (53.3%) dentists experienced the oral surgery against patients with angiogenesis inhibitors. Regarding the contents of oral surgery, tooth extraction was most frequently performed by 94 dentists. Among them, 20 (21.3%) experienced postoperative complications after the tooth extraction. Among 5 dentists who performed oral surgery such as dental implant insertion and periodontal surgery, 2 experienced postoperative complications. Before the oral surgery, 37 dentists (32.7%) asked physician to postpone angiogenesis inhibitor or to change these drugs to the alternatives. During the discontinuation of angiogenesis inhibitors, tumor progression was observed in 2 patients.

Regarding the oral adverse events including dental treatment-related complications associated with angiogenesis inhibitors, 79 cases were investigated precisely. In patients with angiogenesis inhibitors, most patients (73.4%, 58 patients) were administrated bevacizumab and 13 (16.5%) were administrated everolimus (Table 1). In 53 patients with the average administration period of angiogenesis inhibitors was 14.0 ± 10.0 months (range; 1–48 months) (Table 2). As the dental treatment-related complications, delayed wound healing was most seen in 45 patients (57.0%), osteonecrosis of the jaw in 25 (31.6%), postoperative wound infection in 11 (13.9%), and stomatitis in 9 (11.4%) (Table 3). Regarding the risk factors for the oral adverse events including dental treatment-related complications associated with angiogenesis inhibitors, the combination therapy with other anticancer drug was most seen in 47 patients (59.5%), corticosteroids use in 12 (15.2%), and diabetes mellitus in 7 (8.9%) (Table 4). Among 79 cases, complications which was occurred obviously by dental treatments were 53 cases (67.1%). In 53 cases of dental treatments, tooth extraction was mainly in 51 cases (96.2%), and periodontal surgery in 1 (1.9%). The period until the onset of dental treatment-related complications was 3.5 ± 3.5 months (range; 0–12 months). The discontinuation of angiogenesis inhibitors was performed in 13 cases (24.5%). Among the 53 cases which was performed the dental treatments, marginal periodontitis was most seen in 17 cases (32.1%) (Table 5). Apical periodontitis in 7 (13.2%), and root fracture in 6 (11.3%). The clinical characteristics of marginal periodontitis cases revealed that average depth of periodontal pocket was 7.1 ± 1.9 mm (range; 4–10 mm) and 12 of 17 (70.6%) cases had the history of acute inflammation. In apical periodontitis cases, the average size of apical lesion was 4.3 ± 2.6 mm (range; 2–12 mm), and 2 of 5 cases (40.0%) had the history of acute inflammation. In 6 cases of root fracture, the history of acute inflammation was seen in 5 cases (83.3%). In X-ray findings, radiopaque findings around the tooth was observed in 22 cases (41.5%)

Table 1 The number and percentage of angiogenesis inhibitors in dental treatment-related complications (n = 79).

Angiogenesis inhibitor	Number (%)
Bevacizumab	58 (73.4)
Everolimus	13 (16.5)
Sorafenib Tosilate	4 (5.1)
Ramucirumab	1 (1.3)
Sunitinib	1 (1.3)
Aflibercept Beta	1 (1.3)
Lenvatinib	1 (1.3)
Lenvatinib + Everolimus	1 (1.3)

Table 2 The demographic data of the patients with dental treatment-related complications associated with angiogenesis inhibitors (n = 53).

Variable	Number (%)
Average administration period of angiogenesis inhibitors	14.0 ± 10.0 months (range:1–48)
Correlation between dental treatment and dental treatment-related complications associated with angiogenesis inhibitors	
No	26 (32.9)
Yes	53 (67.1)
Correlation between oral surgery and dental treatment-related complications associated with angiogenesis inhibitors	
Tooth extraction	51 (96.2)
Periodontal surgery	1 (1.9)
Other	1 (1.9)
Average period to the onset of the dental treatment-related complications associated with angiogenesis inhibitors	3.5 ± 3.5 months (range: 0–12)
Discontinuation of angiogenesis inhibitors	
No	38 (71.7)
Yes	13 (24.5)
Unknown	2 (3.8)

Discussion

The angiogenesis inhibitors includes monoclonal antibodies which directly effect on vascular endothelial growth factor

Table 3 The number and percentage of dental treatment-related complications in patients with angiogenesis inhibitors (n = 95, overlapping distribution).

Symptom	Number (%)
Delayed wound healing	45 (57.0)
Osteonecrosis of the jaws	25 (31.6)
Postoperative wound infection	11 (13.9)
Stomatitis	9 (11.4)
Postoperative hemorrhage	4 (5.1)
Postoperative pain	1 (1.3)

Table 4 The number and percentage of risk factors for dental treatment-related complications (n = 89, overlapping distribution).

Risk factor	Number (%)
Anticancer drug	47 (59.5)
Corticosteroids	12 (15.2)
Diabetes mellitus	7 (8.9)
High-dose anti-resorptive agent	7 (8.9)
Immunosuppressive agent	5 (6.3)
Chronic renal failure	3 (3.8)
Unknown	8 (9.0)

Table 5 Clinical diagnosis for dental treatments (n = 53).

Clinical diagnosis	Number (%)	Clinical findings	History of acute inflammation
Marginal periodontitis	17 (32.1)	Median periodontal pocket depth 7.1 ± 1.9 mm (range:4–10 mm)	12/17 cases (70.6%)
Apical Periodontitis	7 (13.2)	Median size of apical lesion 4.3 ± 2.6 mm (range:2–12 mm)	5/7 cases (71.4%)
Root fracture	6 (11.3)	–	5/6 cases (83.3%)
Denture ulcer	2 (3.8)	–	Unknown
Pericoronitis	1 (1.9)	–	Unknown
Unknown	20 (37.7)	–	Unknown

(VEGF), such as bevacizumab and ramucirumab, and tyrosine kinase inhibitors which effect on VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and other signaling pathways, such as sunitinib, sorafenib, pazopanib, axitinib, and cabozantinib.[1] In Japan, bevacizumab was firstly approved for advanced/metastatic colorectal cancer in April 2007. However, in the Japanese registration trials and large cohort studies conducted in Asia, the limitation was small number of patients.[4] In a Japanese post-approval surveillance study, since hypertension was reported as the most common adverse drug reaction with 13.1%, hemorrhage with 10.5%, the incidences of serious adverse events were low.[4] However, there a few reports regarding the oral adverse events in Japanese patients with angiogenesis inhibitors, which based on small number of patients at single institute or case report.[8,7] Therefore, the aim of this study was to investigate the dental treatment-related complications in Japanese cancer patients with angiogenesis inhibitors, based on the nation-wide questionnaire survey which was conducted by the Japanese Society of Dentistry for Medically Compromised Patient.

Regarding the oral adverse events in the patients with angiogenesis inhibitors administration, although stomatitis, xerostomia, dysgeusia have been known widely, the prevalence of these oral adverse events remains unclear, especially in Japanese cancer patients. Additionally, the osteonecrosis of the jaw was reported in patients with angiogenesis inhibitors administration.[5,6,10] In this nationwide questionnaire survey, the dental treatment-related complications was observed in 79 patients with angiogenesis inhibitors, although the precise prevalence of these complications remains unclear. Among 79 patients, 58 patients were received anti-VEGF monoclonal antibody, bevacizumab. Bevacizumab-associated stomatitis has been reported uncommon.[1] However, in the review of the anti-angiogenic agent-related osteonecrosis of the jaws, bevacizumab was most commonly found in 58% in cases.[6] Bevacizumab prevents VEGF to bind onto endothelial cells, which results in antiangiogenetic effects.[6] On the other hands, VEGF has been reported to have important roles in wound healing processes with the regulation of angiogenesis, the improvements of re-epithelization, and collagen deposition.[11,12] Since the VEGF exists also in the saliva, it has the important roles in cell repairing and wound healing of oral mucosa.[13] The severe aphthous stomatitis was seen in the patients with low VEGF concentration in the saliva.[14] In this survey, delayed wound healing, osteonecrosis of the jaw, and postoperative wound infection were mainly seen as dental treatment related complications, and this might be due to the inhibitory effects of these drugs on wound healing process.

In this study, the osteonecrosis of the jaw was seen in 25 patients (31.6%). In a meta-analysis of the advanced breast cancer patients, the overall incidence of osteonecrosis of the jaw was 0.2% in patients treated with bevacizumab alone, and 0.9% with the combination with bisphosphonates.[5] In this survey, since 7 patients were treated with the combination of anti-angiogenesis inhibitors and high dose bisphosphonates, the combination therapy with these drugs might be one of the potential risk factor for dental treatment related complications. Because the combination with anticancer drugs was seen in 47 patients (59.5%), the immune-suppressive and myelosuppression under chemotherapy might be a risk factor for post-dental treatment complications.

The dental treatment-related complications were mainly triggered by the tooth extraction (96.2%) in this survey. In a meta-analysis of the anti-angiogenic agent-related osteonecrosis of the jaws, since tooth extraction was seen in 50% of cases as triggering factors, invasive dental procedures such as tooth extraction was one of the major risk factors for onset of angiogenesis inhibitors-related osteonecrosis of the jaws.[6] In a previous report, the extraction of tooth with pre-existing local inflammation was reported a risk of medication-related osteonecrosis of the jaws after tooth extraction.[15] In this study, since the causes of dental treatments were mainly marginal

periodontitis, apical periodontitis, and root fracture, pre-existing local inflammation might be also one of risk factors for anti-angiogenesis related osteonecrosis of the jaws after tooth extraction.

The strong point of this study was the first investigation of dental-treatments related complications in Japanese cancer patients based on the nation-wide questionnaire survey which was conducted by the Japanese Society of Dentistry for Medically Compromised Patient. However, this study had some limitations. Due to the retrospective nature of this study with the questionnaire survey, it was difficult to determine the prevalence of dental treatment-related complications in patients with angiogenesis inhibitors. Additionally, because this study had no control group, the statistical analysis was also difficult to investigate the risk factor for dental treatment-related complications. Therefore, the further investigation will be needed with prospective study.

In conclusion, among 212 dentists, 87.3% recognizes the possibility of dental treatment-related complications in patients with angiogenesis inhibitors. The oral adverse events including dental treatment related complications associated with angiogenesis inhibitors was 79 cases. In patients with angiogenesis inhibitors, 73.4% of patients were administrated bevacizumab. The average administration period of angiogenesis inhibitors was 14.0 ± 10.0 months. As the dental treatment related complications, delayed wound healing was most seen in 45 patients (57.0%) and osteonecrosis of the jaw in 25 (31.6%). The triggered factors of complications tooth extraction was tooth extraction in 51 cases (96.2%). The extraction of the tooth with pre-existing inflammation might be suggested one of risk factors for angiogenesis inhibitor-related dental treatment complications.

Declaration of Competing Interest

The authors declare no conflicts of interest associated with this manuscript.

References

1. Vigarios E, Epstein JB, Sibaud V. Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. *Support Care Canc* 2017;25:1713—39.
2. Gerber HP, Ferrara N. Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies. *Cancer Res* 2005;65:671—80.
3. Loriot Y, Perlemuter G, Malka D, et al. Drug insight: gastrointestinal and hepatic adverse effects of molecular-targeted agents in cancer therapy. *Nat Clin Pract Oncol* 2008;5:268—78.
4. Hatake K, Doi T, Uetake H, Takahashi Y, Ishihara Y, Shirao K. Bevacizumab safety in Japanese patients with colorectal cancer. *Jpn J Clin Oncol* 2016;46:234—40.
5. Sivolella S, Lumachi F, Stellini E, Favero L. Denosumab and anti-angiogenetic drug-related osteonecrosis of the jaw: an uncommon but potentially severe disease. *Anticancer Res* 2013;33:1793—7.
6. Caminha RDG, Chicrala GM, Soares Júnior LAV, Santos PSDS. Risk profile for antiangiogenic agent-related osteonecrosis of the jaws. *Einstein (Sao Paulo)* 2019;17:eRW4628.
7. Takahashi H, Sato M, Tsukada K, Tsuchiya S, Tanda S. A retrospective study of oral adverse events with colorectal cancer chemotherapy using bevacizumab. *Gan To Kagaku Ryoho* 2011;38:959—62 [In Japanese, English abstract].
8. Akiyama K, Saito M, Komiyama Y, Tsuchida S, Okubo M, Kawamata H. Clinical observation of the patients with oral adverse events during cancer chemotherapy including molecular targeted drugs. *J Jpn oral Medicine* 2016;22:1—7 [In Japanese, English abstract].
9. Ruggiero SL, Dodson TB, Fantasia J, et al. American association of oral and maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw-2014 update. *J Oral Maxillofac Surg* 2014;72:1938—56.
10. Marino R, Orlandi F, Arecco F, Gandolfo S, Pentenero M. Osteonecrosis of the jaw in a patient receiving cabozantinib. *Aust Dent J* 2015;60:528—31.
11. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. *Physiol Rev* 2003;83:835—70.
12. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. *Wound Repair Regen* 2008;16:585—601.
13. Upile T, Jerjes W, Kafas P, et al. Salivary VEGF: a non-invasive angiogenic and lymphangiogenic proxy in head and neck cancer prognostication. *Int Arch Med* 2009;2:12.
14. Brozovic S, Vucicevic-Boras V, Mravak-Stipetic M, Jukic S, Kleinheinz J, Lukac J. Salivary levels of vascular endothelial growth factor (VEGF) in recurrent aphthous ulceration. *J Oral Pathol Med* 2002;31:106—8.
15. Hasegawa T, Hayashida S, Kondo E, et al. Medication-related osteonecrosis of the jaw after tooth extraction in cancer patients: a multicenter retrospective study. *Osteoporos Int* 2019;30:231—9.