Original Article

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

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KEYWORDS
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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.

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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.

Materials and methods

This study protocol was approved by the Committee on Medical Research of Shinshu University (54490). 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 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 questionnaire 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.

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%)

### Discussion

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

| 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) |

| 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) |
patients were received anti-VEGF monoclonal antibody, bevacizumab. Bevacizumab-associated stomatitis has been reported uncommon. However, in the review of the anti-angiogenic agent-related osteonecrosis of the jaws, bevacizumab was most commonly found in 58% in cases. Bevacizumab prevents VEGF to bind onto endothelial cells, which results in antiangiogenetic effects. 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. Since the VEGF exists also in the saliva, it has the important roles in cell repairing and wound healing of oral mucosa. The severe aphthous stomatitis was seen in the patients with low VEGF concentration in the saliva. 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. 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. 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. In this study, since the causes of dental treatments were mainly marginal

| 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. 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. 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 incidence of serious adverse events were low. 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. Therefore, the aim of this study was to investigate the dental treatment-related complications in Japanese 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. In this nation-wide 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
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.

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