Is Administration of Trastuzumab an Independent Risk Factor for Developing Osteonecrosis of the Jaw Among Metastatic Breast Cancer Patients Under Zoledronic Acid Treatment?

Kezban Nur Pilanci, MD, Gul Alco, MD, Cetin Ordu, MD, Dauren Sarsenov, MD, Filiz Celebi, MD, Zeynep Erdogan, MD, Filiz Agacayak, MD, Serkan Ilgun, MD, Coskun Tecimer, MD, Gokhan Demir, MD, Yesim Eralp, MD, Sait Okkan, MD, and Vahit Ozmen, MD

Abstract: One of the most important adverse effects of zoledronic acid (ZA) is osteonecrosis of the jaw (ONJ). In previous literature, several risk factors have been identified in the development of ONJ. In this study, we aimed to determine the role of trastuzumab, an antiangiogenic agent, as an independent risk factor for the development of this serious side effect.

Our study included 97 patients (mean age: 54 ± 10 years) with breast cancer, recorded in the archives of the Istanbul Florence Nightingale Breast Study Group, who received ZA therapy due to bone metastases between March 2006 and December 2013. We recorded the patients’ ages, weights, duration of treatment with ZA, number of ZA infusions, dental procedures, anticancer treatments (chemotherapy, aromatase inhibitor, trastuzumab), the presence of diabetes mellitus or renal dysfunction, and smoking habits.

Thirteen patients (13.40%) had developed ONJ. Among the patients with ONJ, the mean time of exposure to ZA was 41 months (range: 13–82) and the mean number of ZA infusions was 38 (range: 15–56). The duration of treatment with ZA and the use of trastuzumab were observed to be 2 factors that influenced the development of ONJ ($P = 0.049$ and $P = 0.028$, respectively).

The development of ONJ under ZA treatment may be associated solely with the duration of ZA treatment and the concurrent administration of trastuzumab. These findings show that patients who are administered trastuzumab for metastatic breast cancer while undergoing ZA treatment are prone to developing ONJ. Therefore, we recommend intense clinical observation to avoid this particular condition in patients receiving ZA and trastuzumab.

INTRODUCTION

Breast cancer is the most frequently observed type of invasive cancer, affecting approximately 1 million women worldwide and causing bone metastases in 65% to 75% of patients. Bisphosphonates are some of the most effective treatments for preventing complications related to bone metastases. Zoledronic acid (ZA) is the most effective molecule in reducing skeletal-related events (SREs) in patients with breast cancer.

Bisphosphonates inhibit bone resorption and protect bone structure by inhibiting the differentiation of osteoclastic precursors, promoting apoptosis of osteoclasts, and stimulating the secretion of osteoclast inhibitory factor from osteoblasts. One of the most important adverse effects that limit its clinical use is osteonecrosis of the jaw (ONJ). According to the American Oral and Maxillofacial Surgery Association, current therapy or a history of therapy with bisphosphonates, no radiotherapy to the head and neck area, and the presence of exposed necrotic bone in the maxilla and/or mandible for at least 8 weeks support the diagnosis of ONJ. Studies have found the incidence of ONJ to be 1% to 10%. Following the first scientific report published by Marx in 2003 that pointed to a link between bisphosphonates and ONJ, the number of studies focusing on this subject has rapidly increased. Moreover, numerous risk factors for the development of ONJ have also been described (cancer and anticancer therapy, dental risk factors, corticosteroids, alcohol and tobacco abuse, anemia, diabetes, obesity, and renal impairment).

Trastuzumab is one of the most widely used agents for the management of all metastatic breast cancers with human epidermal growth factor receptor 2 (HER2) overexpression as indicated by 3+ HER2 immunostaining or gene amplification on the fluorescence in situ hybridization test. The development of ONJ has been reported to have occurred in 2 patients with concurrent use of trastuzumab and bisphosphonates. However, in both these reports, the authors did not correlate the occurrence of ONJ in their patients with the combined use of...
these 2 agents. In the present study, we made an attempt to analyze the use of trastuzumab as an independent risk factor for the development of ONJ in metastatic breast cancer patients undergoing ZA treatment.

**PATIENTS AND METHOD**

Patient data were identified retrospectively from the archives of the Florence Nightingale Breast Study Group, Istanbul, between March 2006 and December 2013. In this study, we included 97 consecutive patients with metastatic breast cancer who had bone metastases and underwent treatment with ZA. Patients with <12 months of follow-up and radiotherapy to the head and neck area were excluded from the study. Patients were analyzed according to their characteristics (age, weight, number of ZA infusions, time of exposure to ZA [months], smoking habits, dental procedures, receiving aromatase inhibitors [AI], receiving chemotherapy [CT], trastuzumab treatment, and renal dysfunction). The diagnosis of bone metastasis was based on radiologic methods such as direct radiography, bone scintigraphy, and positron emission tomography-computed tomography. The standard therapy involved intravenous infusion of 4 mg every 3 to 4 weeks (in 150 cc of saline within 15 minutes).

Patients were examined by a dentist every 6 to 12 months and all dental procedures performed before the initiation of therapy with ZA and during the therapy period were recorded. Patients with suspected ONJ were referred to a maxillofacial surgeon. The diagnosis of the ONJ was made through clinical and radiologic examinations, and biopsies were performed when necessary. The study was approved by the Bilim University ethics committee (Decision no: 27-200).

**Statistical Evaluation**

Statistical analysis was performed using the Statistical Package for Social Sciences Social Sciences (SPSS Inc., Chicago, IL) for Windows 17.0 software. During the evaluation of the study data, in addition to the descriptive statistical methods (mean, median, number, and percentage), the χ² test was employed for the qualitative comparison of the development of ONJ along with the patient and disease-related characteristics, whereas quantitative comparisons were made through the independent samples t test. Evaluation of the independent parameters related to the development of ONJ was based on the multiple logistical regression (forward stepwise) model. The results were assessed within a 95% confidence interval, and a value of $P < 0.05$ was accepted as statistically significant.

**RESULTS**

The median age of the patients was 55 years (range: 33–74). The mean time of exposure to ZA was $37 ± 18$ months (range: 13–87) and the mean number of ZA infusions was $35 ± 16$ (range: 10–73) (Table 1).

Thirteen patients (13.40%) developed ONJ. The median age of the patients who developed ONJ was 61 years (range: 39–73). The mean time of exposure to therapy with ZA was $47 ± 22$ months (range: 13–87), and the mean number of intravenous ZA infusions was $41 ± 15$ (range: 15–66). The 8 (62%) of 13 patients developed ONJ had received trastuzumab, but 5 (38%) of them had not received. Among these patients, 1 patient (7.69%) was asymptomatic, whereas 9 patients (69.24%) were diagnosed through clinical and radiologic examinations. In 4 patients (30.76%), the probability of metastasis was ruled out by biopsy. There were 15 lesions in total; 11 patients had single lesions whereas 2 patients had double lesions. Six of the lesions were detected in the mandible and 5 in the maxilla, whereas 2 involved both the maxilla and the mandible (Table 2).

None of the patients received chronic corticosteroid therapy. When the diagnosis of ONJ was made, 9 patients (69.20%) were under treatment with AIs, 8 patients (62%) were

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**TABLE 1. Patient Characteristics**

| Characteristic                        | Total (n = 97) Mean ± SD | No ONJ (n = 84) Mean ± SD | ONJ (n = 13) Mean ± SD | $P^i$  |
|--------------------------------------|--------------------------|---------------------------|------------------------|-------|
| Age, y                               | 54 ± 10                  | 54 ± 10                   | 57 ± 10                | 0.241 |
| Weight, kg                           | 69 ± 13                  | 68 ± 13                   | 73 ± 10                | 0.218 |
| Number of ZA infusions               | 35 ± 16                  | 34 ± 16                   | 41 ± 15                | 0.111 |
| Time of exposure to ZA, mo           | 37 ± 18                  | 36 ± 17                   | 47 ± 22                | 0.026*|

| Smoking habit                        | 30 32                   | 26 31                     | 4 31                   | 0.989 |
| Tooth extraction                     | 87 93                   | 74 88                     | 13 100                 | 0.349 |
| Root canal treatment                 | 49 52                   | 41 49                     | 8 62                   | 0.393 |
| Dentures                             | 48 51                   | 40 48                     | 8 62                   | 0.350 |
| DM                                   | 18 19                   | 16 19                     | 2 15                   | 0.752 |
| AI                                   | 67 71                   | 57 68                     | 10 77                  | 0.510 |
| CT                                   | 72 77                   | 61 73                     | 11 85                  | 0.357 |
| Trastuzumab treatment                | 31 33                   | 23 27                     | 8 62                   | 0.023*|
| Renal dysfunction                    | 22 23                   | 20 24                     | 2 15                   | 0.500 |

$Ai$ = aromatase inhibitor, $CT$ = chemotherapy, $DM$ = diabetes mellitus, ONJ = osteonecrosis of the jaw, SD = standard deviation, ZA = zoledronic acid.

* $P < 0.05$.

† Independent samples t test.

‡ Fisher exact test.
TABLE 2. Characteristics of Patients With ONJ

| Number of ZA Infusions | Time of Exposure to ZA, mo | Location of ONJ | Concurrent Anticancer Treatment | Dental Procedures | Symptom | Surgery | Antibiotics |
|------------------------|---------------------------|----------------|---------------------------------|-------------------|--------|---------|------------|
| 32                     | 32                        | Maxilla, mandible | Aromatase inhibitor, trastuzumab | Tooth extraction, dentures | Yes     | None    | Amoxicillin |
| 30                     | 26                        | Mandible         | Chemotherapy, trastuzumab       | Tooth extraction, dentures | Yes     | Yes     | Cefazolin   |
| 46                     | 78                        | Maxilla          | Aromatase inhibitor, trastuzumab | Tooth extraction, dentures | Yes     | None    | Amoxicillin |
| 44                     | 48                        | Maxilla          | Aromatase inhibitor trastuzumab | Tooth extraction, root canal treatment, dentures | Yes     | None    | Penicillin  |
| 15                     | 13                        | Maxilla, mandible | Aromatase inhibitor             | Tooth extraction, root canal treatment, dentures | Yes     | None    | Penicillin  |
| 34                     | 36                        | Maxilla          | Chemotherapy, trastuzumab       | Tooth extraction, root canal treatment, dentures | Yes     | None    | Amoxicillin |
| 45                     | 38                        | Mandible         | Chemotherapy, trastuzumab       | Tooth extraction      | Yes     | None    | Amoxicillin |
| 62                     | 55                        | Maxilla          | Aromatase inhibitor             | Tooth extraction, root canal treatment | Yes     | Yes     | Penicillin  |
| 35                     | 32                        | Mandible         | Aromatase inhibitor             | Tooth extraction, root canal treatment | Yes     | Yes     | Amoxicillin |
| 66                     | 62                        | Mandible         | Trastuzumab                    | Tooth extraction, root canal treatment | Yes     | None    | Amoxicillin |
| 38                     | 41                        | Mandible         | Aromatase inhibitor             | Tooth extraction, root | Yes     | None    | Cefazolin   |

ONJ = osteonecrosis of the jaw, ZA = zoledronic acid.

taking trastuzumab, and 3 patients (23%) were receiving systemic CT. All of the patients with ONJ had undergone dental procedures. The dental procedures included tooth extractions in all patients, root canal treatment in 8 patients, and dentures in 7 patients. Following conservative treatment, 4 patients (30.76%) needed surgery (Table 2).

There was no association of the development of ONJ with age ($P = 0.241$), weight ($P = 0.218$), number of ZA infusions ($P = 0.111$), smoking habits ($P = 0.989$), dental procedures (tooth extraction [$P = 0.349$], root canal treatment [$P = 0.393$], dentures [$P = 0.350$]), diabetes mellitus ($P = 0.752$), receiving AI ($P = 0.510$), receiving CT ($P = 0.357$), or renal dysfunction ($P = 0.500$).

Duration of exposure to ZA and the use of trastuzumab were associated with the development of ONJ ($P = 0.049$ and $P = 0.028$, respectively) (Table 3). No patient who received ZA for $<13$ months developed ONJ.

TABLE 3. Multivariate Logistic Regression Analysis (Forward Stepwise)

| Influential Factors in the Development of ONJ | OR (95% CI) | $P$ |
|----------------------------------------------|-------------|-----|
| Trastuzumab use                               | 4.038 (1.159–14.069) | 0.028 |
| ZA use, mo                                    | 1.032 (1.00–1.065)   | 0.049 |

Cl = confidence interval, ONJ = osteonecrosis of the jaw, OR = odds ratio, ZA = zoledronic acid.

DISCUSSION

Unless there is an interfering condition, bisphosphonates are currently regarded as the standard therapy for SREs in the treatment of bone metastases. ONJ is one of the most important complications associated with bisphosphonate therapy used in patients who have breast cancer with bone metastases. This condition is due to accumulation of bisphosphonates in great amounts both in the alveolar bone and the surrounding soft tissue. This increases the risk of avascular necrosis, which, in addition to disruption of the mucosal barrier mediated by stimulating the apoptosis of keratinocytes, delays wound healing and tissue repair by inhibiting the formation of blood vessels through antiangiogenic effects. Trastuzumab is another antiangiogenic agent particularly indicated in metastatic breast cancers with HER2 overexpression. Trastuzumab has been demonstrated to inhibit angiogenesis and this effect is believed to occur through the expression of antiangiogenic factors and inhibition of proangiogenic factors. Combining bisphosphonates with antiangiogenic agents has been suggested to induce ONJ more frequently than using bisphosphonates alone. In this article, we focused on the impact of trastuzumab as well as the other factors in the development of ONJ in metastatic breast cancer patients receiving ZA.

Although ONJ is mostly associated with dental procedures, other factors that play a role in its pathogenesis are listed in some studies: duration of exposure to ZA, number of infusions, type of bisphosphonate, route of administration (oral, intravenous), concurrent CT, chronic use of corticosteroids, poor oral hygiene, smoking, and poorly fitting dentures. Although symptoms including orofacial pain, puffy face, and malodorous
discharge during treatment with bisphosphonates support the diagnosis of ONJ, it may be necessary to rule out any metastases to the orofacial bones. However, because of the risk of diagnostic biopsy of the bone that may lead to a compromise in wound healing, the diagnosis is usually based on clinical and radiologic examinations.22

In a retrospective study by Bamias et al,12 the most important risk factors suggested to increase the risk of development of ONJ were found to be duration of exposure to treatment, the number of infusions, dental procedures, and the type of bisphosphonate used. The duration of bisphosphonate treatment has also been marked as a risk factor for the development of ONJ in other clinical studies.10,11,23 In our study, duration of ZA treatment was detected as a significant risk factor in the development of ONJ, which strengthens the outcomes of the above studies.

Although a relationship between dental procedures and ONJ was observed in certain studies,24 no statistically significant correlation was observed between dental procedures and ONJ in our study. The fact that the majority of the patients in which no ONJ occurred had also undergone dental procedures may have led to this result.

Antiangiogenic agents that are used with increasing frequency may enhance the risk of ONJ, especially when used concurrently with bisphosphonates. For instance, there have been recent reports of patients with ONJ caused by antiangiogenic agents such as sunitinib (multikinase inhibitors), bevacizumab (a monoclonal antibody that targets vascular endothelial growth factor), and everolimus (inhibitor of mammalian target of rapamycin), with or without bisphosphonates.25–27

Trastuzumab is also an antiangiogenic agent that is especially indicated in breast cancer treatment.15 There have been no reports in the literature on development of ONJ solely due to trastuzumab treatment. There have been a few cases of development of ONJ during concurrent treatment with bisphosphonates and trastuzumab; however, an association of trastuzumab with the occurrence of ONJ has not been clearly stated in these reports.14,15 Moreover, in a study by Hoff et al,28 a large number of patients were evaluated for ONJ incidence and risk factors regarding the development of ONJ. No relationship was observed between ONJ and treatment with trastuzumab, anthracycline, tamoxifen, taxane, or AIs.29–30 In agreement with our findings, the rate of treatment with trastuzumab in patients with ONJ was observed to be significantly higher than in those without ONJ (P = 0.028).

The combination of ZA and other antiangiogenic agents (sunitinib, everolimus, bevacizumab) has recently been revealed to be associated with an ONJ rate of up to 16%.21,31–36 In addition, treatment with bevacizumab alone has been correlated to ONJ in a few case presentations.37 We suggest that our study brings up the matter of the effect of trastuzumab on ONJ when it is combined with ZA, as we observed a 13.6% occurrence rate of ONJ, which matches the previous reports.6,7 The outcomes of our study may indicate that trastuzumab has antiangiogenic potency similar to that of other agents.

CONCLUSION

This study evaluated data obtained from patients with isolated metastatic breast cancer, whose files and treatments were regularly followed up. In this study, the development of ONJ was associated with longer treatment and higher cumulative doses of intravenous ZA therapy, and with concurrent treatment of ZA and trastuzumab in breast cancer patients. ZA is widely used in the treatment of bone metastases due to breast cancer. The increased risk of ONJ should be kept in mind and all preemptive measures should be taken, especially when ZA is used with trastuzumab. The retrospective nature of the study and the statistical analysis of a small number of cases of ONJ are limitations of our study. We suggest that prospective studies should be performed to confirm these results, and more careful studies are also needed to define the minimum dose and duration of therapy with bisphosphonates necessary to prevent skeletal complications of malignancy.

ACKNOWLEDGMENTS

The authors would like to thank David Chapman for the medical writing and editing assistance provided in the preparation of this article, and Atilla Bozdogan, PhD, for performing the statistical analysis.

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