

MEETING REPORTS

Osteonecrosis of the Jaw: Meeting Report from Skeletal Complications of Malignancy V

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Osteonecrosis of the Jaw (ONJ) (Session 9)

Since the earliest case suggesting an association of osteonecrosis of the jaw (ONJ) with bisphosphonate (BP) use in 2003, many other ONJ cases have been documented, highlighting the need for clarification of the association between ONJ and BP treatment. Whether BPs are causal in the development of ONJ remains to be determined. Extensive work has been devoted to the re-evaluation of reported cases, generation of guidelines for BP treatment, and defining quantitative diagnostic criteria for ONJ via a stage/grading system and case definition, through efforts of the American Association of Oral and Maxillofacial Surgeons, an ASBMR Task Force, and other groups (1-4).

A thorough review of the pharmacology of BPs was presented by M. Rogers. BPs are synthetic analogs of cellular inorganic pyrophosphates with a P-C-P backbone structure and have been in use for almost 30 years. The two variable sidechains on the central carbon atom confer the compound's binding affinity to bone and antiresorptive properties. Progressive chemical modifications expanded the original simple, non-nitrogen-containing BPs into a series of nitrogen-containing compounds with increasing binding affinity to bone and antiresorptive potency. The first generation of BPs, etidronate, tiludronate and clodronate, exert their action by being incorporated into osteoclasts and forming a cytotoxic metabolite that closely resembles adenosine 5'-triphosphate (ATP). This toxic analog of ATP cannot be degraded and causes apoptosis of osteoclasts (5). Nitrogen-containing BPs can be divided

into two categories: alendronate and pamidronate contain the primary amine moiety and others such as risedronate, zoledronate and ibandronate contain nitrogen as tertiary amines (6). These BPs inhibit the activity of farnesyl pyrophosphate synthase (FPPS), an enzyme in the mevalonate (cholesterol) pathway whose crystal structure was recently elucidated (4;7). Blocking FPPS in turn prevents proper post-translational modification of the small GTPase cell signaling molecules in osteoclasts (8). Nitrogen-containing BPs are potent FPP synthase inhibitors since they nearly irreversibly bind to the enzyme. N-BPs also inhibit geranylgeranyl diphosphate synthase (GGPPS) (9). The impact of BPs may not be totally selective for osteoclasts. For example, BPs cause similar effects in other cell types including tumor cells (10) and T-cells (11). Once incorporated into bone, BPs can reside in vascular channels and osteocyte canaliculi with long-term bioavailability up to years. Hence, the benefits as well as risks associated with BP use could be prolonged.

Several presentations at the meeting updated the incidence rates of BP-associated ONJ in breast cancer, multiple myeloma and prostate cancer patients. The overall incidence is 0.5-10% in patients with cancer being treated with high doses of intravenous BPs, specifically 0.6-1.1% in breast cancer (12), 3.5-10% in multiple myeloma (2) and about 6% in prostate cancer patients, though according to a poster presentation (13), the incidence of BP-associated ONJ could be up to 17% (nine out of 54). However, the sample size in that study was relatively small and the patients' previous medications and dental histories were complex. The R. Coleman

update on the AZURE clinical trial was discussed. This randomized clinical trial of more than 3,000 women with stage II/III breast cancer is investigating whether adjuvant zoledronate could improve the disease-free and bone metastasis-free survival. To date, there have been 9 cases of ONJ in the study and they have all been in the zoledronate treatment arm (14).

It is difficult to precisely identify predisposing factors associated with ONJ development, though several analyses strongly suggested an association between the use of BPs and the occurrence of ONJ. One study described 17 among 252 patients (6.7%) receiving BPs who developed ONJ: 11 of 111 with multiple myeloma (9.9%), 2 of 70 with breast cancer (2.9%), and 3 of 46 with prostate cancer (6.5%) (15). The incidence of ONJ increased with time to exposure from 1.5% among patients treated for 4 to 12 months to 7.7% for treatment for 37 to 48 months. The cumulative hazard was significantly higher with zoledronate compared with pamidronate alone or pamidronate and zoledronate sequentially. All but two patients with ONJ had a history of dental procedures within the last year or denture use (15). Another study retrospectively analyzed the characteristics of 35 patients who exhibited ONJ and 24 of them developed ONJ 20-60 months after initial BP treatment (16). The time for the onset of ONJ was significantly shorter for patients treated with zoledronate alone than for those treated with pamidronate followed by zoledronate. According to these studies, other than duration of BP therapy, the type of BP may also play a role and previous dental procedures may be a precipitating factor.

The dosage applied in BP therapy could be a risk factor since the rate of ONJ associated with oral BP therapy for osteoporosis is much lower and the incidence estimated in the range of 0.0001 to 0.001% (3). In a recent clinical study of a large number of women with osteoporosis receiving a BP, no spontaneous ONJ was reported (17). In addition, blinded adjudication of the safety database yielded one case in the zoledronate group and one in the placebo group, suggesting that the risk of ONJ in women with postmenopausal

osteoporosis is very low and that this disorder may occur without BP treatment. A once-yearly regimen with intravenous zoledronate does not appear to affect the frequency of this adverse event in osteoporosis patients (17).

The apparent selective necrosis at the maxilla and mandible may be a reflection of the unique environment of the oral cavity in which more than 500 species of bacteria may reside (18). The bones of the oral cavity are different than other skeletal sites from their early development, forming by intramembranous versus endochondral bone formation. The mandible, reported to be a more frequent site of ONJ than the maxilla, consists of dense cortical bone with relatively less trabecular/cortical bone than other skeletal sites. After tooth extraction or osseous trauma, bone heals with osteoclastic activity at the site of the wounded bone margins followed by the development of immature woven bone that is subsequently remodeled by osteoclasts to a mature lamellar bone. The bones of the oral cavity are covered by thin mucosa that could be easily traumatized and has been speculated to be prone to BP-associated soft tissue toxicity (19). The anti-angiogenic effects of BPs may compromise the vascular supply in addition to inhibiting osteoclasts and thus increase the risk for osteonecrosis to develop at sites of trauma; however it is not clear that the anti-angiogenic effect of BPs is different in the jaws than in other skeletal sites. A poster presentation (13) showed that patients with ONJ all had received a full dose of bevacizumab (an anti-angiogenic agent), which suggested that the risk for ONJ may be higher with patients using anti-angiogenic agents. A recent report describes two cases of ONJ that were found in patients who had metastases to the jaw (20). Although an uncommon site (1% of cancer patients), metastasis to the jaw does occur (21), and raises a new concern. Could ONJ be portraying underlying skeletal metastasis to the jaw?

At this moment, sufficient data, from both clinical and laboratory settings, are still lacking to define the relationship and mechanisms of BP use and ONJ. Whether

zoledronate or other BPs should be discontinued once ONJ occurs is still under debate, with no strong evidence existing for discontinuing them. BP infusions significantly decrease skeletal-related events and improve quality of life (22). This makes health care providers and patients hesitant to cease BPs when ONJ occurs. In fact, one case was discussed by J. Berenson suggesting ONJ was reduced with zoledronate therapy. A 58-year-old patient with multiple myeloma developed severe bilateral upper mouth pain after pamidronate treatment and was diagnosed with ONJ. Interestingly, the oral necrosis resolved 3 months after switching to zoledronate treatment. In another multiple myeloma case, a patient with hypercalcemia and fractures had zoledronate treatment discontinued because of ONJ. Unfortunately, the ONJ still progressed. It may be of benefit to consider alternative strategies to control the development of ONJ without losing the benefits of BP treatment. One resolution that has been presented as beneficial to a subset of osteoporosis patients with osteonecrosis associated with oral BP treatment is intermittent low-dose PTH (23). However, its application for patients with skeletal metastasis would be inappropriate due to contraindications in patients with cancer. Another case series report has proposed the application of platelet-derived growth factors topically to stimulate wound healing (24).

Identification of a predictive marker for ONJ would greatly help early diagnosis and prevention. Extremely low bone resorption levels were hypothesized to be a causal factor of failure in oral trauma healing and ONJ (25). However, there was no evidence of low resorptive markers in the patients who developed ONJ on intravenous BPs as reported in a poster presentation (26). This questions the applicability of biomarkers of systemic bone resorption being used as prognostic indicators of ONJ development.

Numerous questions were raised in this session relative to ONJ and BP therapy. How do bones of the oral cavity differ in anatomy, physiology, and response to BPs vs. other skeletal sites? What are the most accurate diagnostic approaches to identify

ONJ and what signs, factors, or co-morbid conditions can be used to predict who will develop ONJ? What is the role of microflora in BP-associated ONJ? What is the role of soft tissue toxicity? Is there an association between metastasis to the jaw and ONJ lesions? How can we minimize the risk of ONJ and still reap the strong therapeutic benefits of BPs? More studies are needed to elucidate the mechanisms, to determine the incidence and risk factors underlying ONJ, and to identify the most appropriate therapeutic approaches for patients with skeletal metastases and BP-associated ONJ.

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