Osteonecrosis of the jaw under bisphosphonate and antiangiogenic therapies: cumulative toxicity profile?

Bisphosphonates are standard treatment of patients with bone metastases but are associated with the serious complication of osteonecrosis of the jaw (ONJ), which is characterized by intraoral lesions exposing necrotic bone [1]. The estimated prevalence of i.v. bisphosphonate-associated ONJ in cancer patients is as high as 6%–10% [1]. In a retrospective analysis, ONJ occurred in 2% of patients treated with bevacizumab and bisphosphonates compared with 1.1% of patients receiving bisphosphonates alone [2]. However, no causal role of bevacizumab has been identified since no patient receiving bevacizumab alone had ONJ [2]. We read with great interest the first case report of ONJ related to bevacizumab [3]. Given that the mechanism of action of bisphosphonates may be attributable in part to an antiangiogenic effect [4, 5], an additive toxic effect of antiangiogenic drugs in patients...
receiving bisphosphonates may explain the two cases of ONJ observed in our centers.

Both patients received i.v. zoledronate 4 mg every 3 weeks, given for the treatment of bone metastases in our female breast cancer patient (patient 1) and of hypercalcemia in our male renal cell carcinoma patient (patient 2). Patient 1 was switched to oral clodronate after 4 months on zoledronate. She had been on clodronate for 15 months and patient 2 had been on zoledronate for 19 months when ONJ occurred. Patient 1 had received bevacizumab for 2–3 months and patient 2 had received sunitinib for 14 months before diagnosis of ONJ. Both died with ongoing ONJ.

Zoledronate has been implicated in >90% of ONJ cases whereas there is only sparse cases implicating oral clodronate [1, 6]. Since ONJ appeared >1 year after zoledronate administration but bevacizumab was administered in the months before the development of ONJ, we suggest that bevacizumab’s antiangiogenic properties may have been a key factor in the onset of ONJ in patient 1. Since 60% of cases of ONJ are preceded by a dental surgical procedure [1], prior dental extraction could have been an additional factor contributing to the osteonecrosis in patient 1 and also in patient 2. In patient 2, the long duration of zoledronate treatment was probably a key factor contributing to ONJ; however, the concomitant administration of sunitinib may have been the activating factor in the onset.

Although there are no cases to date of sunitinib-related ONJ, the recent case of bevacizumab-related ONJ highlights the potential of antiangiogenic action to contribute to oral mucosal breakdown or impair angiogenesis-dependent bone cell differentiation and formation [2]. With the increased use of antiangiogenic agents in patients with metastatic breast, colon, lung, or kidney cancer, and given that a significant number of these patients could develop bone metastases and be treated with bisphosphonates, oncologists should be aware of the potential for development of ONJ. Prospective studies are required to determine the degree of risk for ONJ associated with bisphosphonates and antiangiogenic drugs and how best this risk can be minimized.

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