Review of: "Long-Term Risk of Medication-Related Osteonecrosis of the Jaw (MRONJ) After Bisphosphonates and/or Denosumab in Metastatic Breast Cancer Patients"

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I found the data published in the authors' commentary clinically relevant and interesting. They made an effort to collect the available information concerning the chosen topic.

The cited retrospective multicenter trial in Tyrol, Austria, conducted between 2000-2020 on metastatic breast cancer patients with bone involvement, studied the results of receiving the RANKL-inhibitor denosumab and bisphosphonates in the observed patient cohort. The authors found an increased cumulative incidence of MRONJ at 6 years when using denosumab, which means a considerably high risk. It must not be forgotten that denosumab is suggested as a prophylactic treatment to prevent SREs, not to treat secondary bone metastases.

- Sequential treatment of bisphosphonates and denosumab needs further evaluation, indeed, as the duration and order of each medication, as well as other interacting therapies, might have a deleterious effect. These results could stand on their own in a separate publication.
- From the POV of a clinician, the diversity of the administered cytotoxic drugs might be a main point as well (considering their huge developments during the last 2 decades). I'm quite convinced about their influence on epithelial and bone metabolism, which results in structural damage. I mean that it makes a difference what kind of treatment we combine with antiresorptive agents. The expected risk of SREs, declining PS, or time to progression depends a lot on primary oncotherapy, too, besides antiresorptive treatment. Some comparisons would enhance the publication.
- Also, patient factors are very important: primarily, dental health (infections, mucositis, etc.) has an important role in developing ONJ with or without radiation therapy or antiresorptive systemic treatments in the medical history.
- The risk of ONJ increases over the years, indeed. But the duration of antiresorptive treatment is not „optimal" most of the time, but limited by regulatory labels and/or side effects (renal impairment or ONJ, first). Dose de-escalation is possible with bisphosphonates but not with denosumab. This issue is still a matter of debate.
- The median time to MRONJ should be specified from the diagnosis of bone metastasis, not the start time of cancer.

The article is interesting, but some points should be further addressed - which doesn't mean a criticism of the quality of the work.

My minor comments do not rule out acceptance.