Commentary

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

Vittorio Fusco[1], Costanza Massarino[1], Maura Rossi[1], Alessio Gambino[2], Antonio Maconi[1], Paolo Giacomo Arduino[2]

1. Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; 2. University of Turin, Italy

Recently published data identified cancer patients with bone metastases receiving continuous monthly antiresorptive drugs (bisphosphonates and/or denosumab) as patients at high risk for Medication-Related Osteonecrosis of the Jaw (MRONJ), even with late onset. A retrospective multicenter study was conducted between 2000 and 2020 at all breast centers across Tyrol (Austria), screening all patients with breast cancer and bone metastases receiving antiresorptive therapy. The MRONJ incidence was found to be considerably high in patients receiving denosumab (11.6%-16.3%), with an elevated cumulative incidence at 6 years.

This commentary underlines some important results of the study and proposes further evaluation of the group of patients receiving a sequence of bisphosphonates and denosumab. Furthermore, other interesting data could come from patients treated in the last decade, receiving more effective anticancer treatments but also more frequently denosumab, in comparison with patients treated in previous years.

Correspondence: papers@team.qeios.com — Qeios will forward to the authors

Brunner et al. are to be commended for their paper "*Incidence of Medication-Related Osteonecrosis of the Jaw in Patients with Breast Cancer During a 20-Year Follow-Up: A Population-Based Multicenter Retrospective Study*" recently published in the Journal of Clinical Oncology[1]. The paper is important for data about the long-term risk of Medication-Related Osteonecrosis of the Jaw (MRONJ) in breast cancer patients with

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bone metastases receiving continuous monthly antiresorptive drugs: bisphosphonates and/or denosumab[1].

Results are interesting for practice, well outside those summarized in the abstract, thanks to the long observation time (20 years) and the accurate follow-up of metastatic breast cancer patients in that population. The Tyrol large "real life" dataset permitted confirmation that the MRONJ risk is higher after continuous monthly denosumab therapy than after monthly bisphosphonate therapy, and that the MRONJ risk increases over years, inducing further doubts about the optimal duration of antiresorptive treatment (an unresolved issue) and pushing attention to possible drug de-escalation or different long-term strategies[2][3].

We wish to point out some aspects that might be usefully clarified.

Firstly, the authors reported in the abstract the median time to MRONJ after treatment initiation, which was shorter for denosumab (4.6 years) than for bisphosphonates alone (5.1 years), whereas it was 8.4 years in patients receiving one bisphosphonate and denosumab sequentially (a particular group, created by the arrival of denosumab into the treatment armamentarium after 2010). We invite readers to pay attention to Table 2, where data are reported as "*Time from cancer diagnosis to MRONJ*" without specifying if it started from the primary cancer diagnosis or the diagnosis of bone metastases: the two moments overlap in patients defined as "with primary metastases" (n=290) but not in those "with secondary metastases" (n=349), and it should be detailed in our opinion. Interestingly, the Q1-Q3 values are 1.6-9.6 for denosumab, 2.9-7.1 for bisphosphonates, and 5.3-9.6 in the sequential group (the authors also reported wide ranges, without extreme numbers, in the table). Those values seem to confirm a common practice experience: MRONJ can sometimes occur very early (in the first 2-3 years of treatment, as reported in randomized trials with short follow-up or "on study" time)[4] but it is often diagnosed several years after the start of treatment[5]. Is the long-term MRONJ risk linked to the length of antiresorptive treatment (i.e., duration and frequency of drug exposure) or linked to the observation time (i.e., patient survival) or both? [3][6]. We lack sufficient "real life" data with long-term observation. Anyway, data from Brunner et al[1] seem to confirm that continuous indefinite (until deterioration or death) denosumab treatment in bone metastatic breast cancer patients highly increases the long-term MRONJ risk, as already known for zoledronic acid[5].

The group of patients receiving a sequence of bisphosphonates and denosumab is very particular. It might be a heterogeneous group, including:

1. Patients receiving bisphosphonates for a long time (and herein at intrinsic “high risk” for MRONJ) [5], in which few denosumab doses might be sufficient to induce the onset of MRONJ (or the emerging of latent MRONJ), and
2. Patients receiving bisphosphonates for a shorter time, in which denosumab was the principal inducer of MRONJ.

To distinguish between those two mechanisms, it could be useful, in our opinion, to read the separate median time (and Q1-Q3) of the two treatments received in the study by all 77 patients receiving sequential therapy, and the duration of the two treatments in 15 patients who developed MRONJ.

Secondly, we agree with Brunner et al. about the cautiousness needed in evaluating differences in time to MRONJ occurrence and in survival[1] across treatment groups in a retrospective study. Anyway, we agree with the authors that differences across survival curves related to treatment groups (figure 3 in Brunner’s paper)[1] could be explained by more effective anticancer treatments received by patients treated in recent years (alongside denosumab as an antiresorptive agent): an analysis of patients divided on the basis of the start year of treatment (for example, in the period 2000-2005, 2006-2010, 2011-2015, and 2016-2020) could be an interesting exploratory evaluation. Incidentally, the possible long survival of metastatic patients after MRONJ onset (several years) was observed also in a North-Western Italian network experience[7].

In conclusion, the choice of a “tailored” antiresorptive treatment may depend on many criteria, including direct (drug) costs, indirect costs, the expected risk of skeletal events, possible early progression and/or worsening of performance status, comorbidities, risk of side effects (including MRONJ), patient’s preference, and life expectancy[3][8][9]. In the absence of large randomized trials comparing different antiresorptive strategies, oncologists have a challenging job if they seek precision medicine for their unique metastatic breast cancer patients. Retrospective data such as those by Brunner et al.[1] are welcome and can be of great value.

References

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Declarations

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