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COMMENTARY

One changing and challenging scenario: the treatment of cancer patients with bone metastases by bisphosphonates and denosumab, the cost–benefit evaluation of different options, and the risk of medication-related osteonecrosis of the jaw (MRONJ)

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Abstract
Antiresorptive drugs (bisphosphonates and denosumab) have become the cornerstone of medical supportive treatment of bone metastases in solid cancer patients. In the beginning, the choice of available antiresorptive agents was limited to bisphosphonates and the treatment options restricted principally to monthly pamidronate and monthly zoledronic acid. Introduction of new antiresorptive therapies (monthly denosumab) and schedules (zoledronic acid every 3 months, upfront or after initial period of monthly infusion) in the last decade increased the range of available options, thus challenging treatment decision making. Direct and indirect costs of very different treatment options are difficult to interpret in a global cost–benefit analysis. In addition, awareness of the increased risk of medication-related osteonecrosis of the jaw (MRONJ) in bone metastatic cancer patients receiving long-term antiresorptive medications is likely to influence therapy choice in the real-life scenario. We discuss the possible threat of MRONJ risk underestimation and the need for long-term risk stratification of patients based on actuarial data, the role of bisphosphonates and denosumab in that scenario, and the emerging role of surgical therapy to successfully cure MRONJ, in the light of the improved quality of life and survival of patients with bone metastases from solid cancers.

Keyword Zoledronic acid; Denosumab; Bone metastases; Solid cancer; Osteonecrosis of the jaw; MRONJ

Several recently published papers in JSCC [1–7] dealt with the prevalence of medication-related osteonecrosis of the jaw (MRONJ) in patients receiving antiresorptive drugs (bisphosphonates and denosumab) and offered us the chance for some considerations about the medical treatment of bone metastases in solid cancer patients.

In our view, uncertainty about drug selection and optimal duration of antiresorptive treatment in patients with bone metastases from solid cancers has increased lately.

The choice of a given antiresorptive medication depends on several aspects:

- available data on the efficacy of antiresorptive medications in the bone metastatic population as a whole, or in specific subgroups (i.e., breast vs. prostate vs. renal cell vs. lung cancer; metastatic cancer subtypes with different aggressiveness);
- direct (drug price for the individuals and/or the health-care systems) and indirect costs (facilities, personnel costs for intravenous or subcutaneous administration, monitoring of calcium and creatinine levels, regular oral health check-ups, etc.);
- risk of short-term and long-term side effects in general and in high-risk subgroups (i.e., elderly people, patients with already partially impaired renal function, patients with compromised oral health, etc.) [8].

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Real-world medical treatment of bone metastases radically changed in the last decade for the following reasons:

- *introduction of denosumab*: 120 mg monthly subcutaneous injection, with several patients already receiving zoledronic acid (or other bisphosphonates), shifted to denosumab, and many others started on denosumab from the beginning [1, 4, 7];
- *introduction of zoledronic acid every 3 months*: (upfront or after a period of monthly treatment) as a possible competitor [9];
- *fear of the rebound effect described following denosumab discontinuation* and its management [10];
- *difference among competing drugs and schedules in term of costs, ease of administration, staff engagement,* etc. [8, 9], with the COVID-19 pandemic likely to interfere with the routine preferences;
- *increased awareness that skeletal-related events (SREs)* — the most used study endpoint in earlier antiresorptive drug trials — *are not fully reliable*, and the introduction of new endpoints, so called symptomatic skeletal events (SSEs) [11];
- *increase of expected survival for a large proportion of bone metastatic cancer patients* due to the recent advances of medical treatment (endocrine therapy, chemotherapy, targeted treatments, immunotherapy);
- *influence of MRONJ risk evaluation*, given the possible MRONJ-related worsening of patient quality of life, *on antiresorptive treatment planning and management*, despite several controversies still exist about MRONJ definition, diagnosis, and therapy [12–14].

At present, three main established therapies (competitors) exist; we should choose from monthly zoledronic acid, monthly denosumab, and quarterly zoledronic acid. To further complicate the picture, combinations of these therapies are possible: shift from zoledronic acid to denosumab or vice versa [1, 4], planned shift from monthly administrations of denosumab or zoledronic acid to quarterly zoledronic acid infusion [1, 4], and suggested strategies of quarterly 120 mg denosumab [9].

Is there a mutual view resulting from recommendations of the Scientific Societies and expert groups? The recently published practice guidelines and recommendations [15–17] did not address all the differences among the competitors otherwise helpful in real-world practice [8, 9], and do not endorse any specific antiresorptive treatment in terms of drug selection and planned duration (Table 1).

Should we outweigh the risk of MRONJ in the clinical practice when we must select the antiresorptive drug and the optimal duration of treatment in patients with bone metastases from solid cancers?

It is our belief that the following underestimated facts should be taken into consideration when choosing the appropriate treatment for patients in the real-world practice:

- MRONJ incidence (or prevalence or frequency) in cancer patients with bone metastases, reported in large trials as of 1–2%, is largely underestimated, for a number of reasons [14];
- MRONJ risk described in recent papers reporting real-life experiences is much higher than previously reported, with values ranging between 5 and 15%, both in patients receiving antiresorptive drugs only and in those receiving antiresorptive together with biological agents (bevacizumab, tyrosine kinase inhibitors, everolimus, etc.) [3, 7, 18–20];
- most recent reports display Kaplan–Meier actuarial curves (data not shown from randomized trials with limited follow-up) that might be helpful to perceive the uprising risk of MRONJ with longer observation times (2–4 years), especially in patients on long-term antiresorptive treatment;
- MRONJ risk seems to increase with longer duration of antiresorptive treatment but also with longer observation time: could it happen independently from the duration of treatment? We need more data after long-term observation, and data about survival of MRONJ patients, to be compared with survival data of other bone metastatic patients [21];
- MRONJ rate increases in bone metastatic cancer patients receiving denosumab as compared with zoledronic acid [3, 7, 18] with even higher rates in patients shifted from zoledronic acid to denosumab [1, 4, 18, 19]. This fact matches the observations made 10 years ago, when many cases of MRONJ were reported in cancer patients shifted from pamidronate to zoledronic acid [1, 4]. At present, we do not know how much of this phenomenon might be linked to denosumab itself or to the length of treatment and/or follow-up;
- we do not know yet how the MRONJ risk might change in patients shifted from monthly denosumab to quarterly zoledronic acid or quarterly denosumab (whereas we have limited but encouraging data after the shift from monthly to quarterly zoledronic acid) [15];
- recently, the surgical treatment of established MRONJ showed some evidence of benefit for patients in terms of curative potential [13]. Healing of MRONJ could be anticipated with surgery and, ideally, favor the restart of the antiresorptive treatment. Nevertheless, not all recommendations endorse the surgical option [12] that still remains object of discussion [13, 14];
- surgical treatment of MRONJ in cancer patients has been contraindicated for a long time, based on their expected

Table 1 Antiresorptive treatment options for bone metastases from solid cancer. Comparison of some recommendations and practice guidelines

Author (ref) organization year	Population	First option(s) of treatment	Other options	Optimal duration of initial treatment	After initial treatment
Van Poznack (15) **ASCO-CCO** 2017	Bone metastatic **breast cancer patients**	**Denosumab 120 mg q4 wks**, or **Pamidronate 90 mg q3-4wks**, or **Zoledronic acid 4 mg q12wks**, or **Zoledronic acid 4 mg q3-4wks** (one drug is not recommended over another)	None	**Indefinitely** (not changed after 2000 ASCO guidelines)	Not applicable
Saylor(16) **ASCO-CCO** 2020	Bone metastatic **prostate cancer patients (castration resistant)**	**Monthly zoledronic acid** or **Monthly denosumab**	None (efficacy of zoledronic acid or denosumab given less often than monthly is not known)	**Optimal safe duration of monthly therapy is not well established** (maximum 24 months in trials)	None
Coleman(17) **ESMO** 2020	Bone metastatic **breast cancer patients**	**Monthly zoledronic acid 4 mg** or **Monthly denosumab 120 mg**	**Oral ibandronate or clodronate** **Zoledronic acid 4 mg 3-monthly** (for only oligometastatic bone disease) (after monthly treatment for at least 3–6 months)	**Indefinitely** (***consider interrupting therapy after 24 months***, for oligometastatic bone disease, and/or in patients in remission)	De-escalation of monthly zoledronic acid to every 12 weeks Not applicable for denosumab Not reported for oral ibandronate and clodronate
Coleman(17) **ESMO** 2020	Bone metastatic **prostate cancer patients (castration resistant)**	**Monthly zoledronic acid 4 mg** or **Monthly denosumab 120 mg**	**Zoledronic acid 4 mg 3-monthly** (for only oligometastatic bone disease) (after monthly treatment for at least 3–6 months)	**Indefinitely** (***consider interrupting therapy after 24 months***, for oligometastatic bone disease, and/or in patients in remission)	De-escalation of monthly zoledronic acid to every 12 weeks Not applicable for denosumab
Coleman(17) **ESMO** 2020	Bone metastatic cancer patients — **other cancers (not breast, not prostate)**	**Monthly zoledronic acid 4 mg** or **Monthly denosumab 120 mg**	**Zoledronic acid 4 mg 3-monthly** (for only oligometastatic bone disease) (after monthly treatment for at least 3–6 months)	**Indefinitely** (***consider interrupting therapy after 24 months***, for oligometastatic bone disease, and/or in patients in remission)	De-escalation of monthly zoledronic acid to every 12 weeks Not applicable for denosumab

Bold and italic characters are to facilitate the readers

Legend: *ASCO* American Society of Clinical Oncology, *CCO* Cancer Care Ontario, *ESMO* European Society of Medical Oncology

short survival and/or supposedly poor cost–benefit analyses. With the improvement of medical anticancer treatments, many MRONJ patients show prolonged survival with performance status and general health conditions good enough to make surgery of MRONJ feasible and adequate during their anticancer treatment [13, 14, 21].

In conclusion, individualized judgment of the appropriate antiresorptive treatment for bone metastatic cancer patients becomes everyday more challenging. Future research should promote large trials to answer the remaining open questions and guide prescribers, in the light of the uniqueness of each patient, to seek a true precision medicine.

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