

Anti-osteoporosis drugs and reduction of mortality in cancer patients

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Osteoporosis and cancer share a complex relationship, with each condition influencing the progression and outcomes of the other.¹ Multiple factors, such as chemo- and hormonal therapies, and the direct invasion of bone tissue by malignant cells contribute to the accelerated bone loss seen in cancer patients.¹ Various anti-osteoporosis drugs, including anti-resorptives such as bisphosphonates, denosumab and selective estrogen receptor modulators (SERMs), and anabolic agents such as teriparatide and romosozumab have demonstrated efficacy in preventing bone loss and reducing fracture risk in non-cancer populations. These medications exert their effects through different mechanisms, such as inhibiting osteoclast activity, modulating hormonal pathways or promoting bone formation.² However, their effectiveness in cancer patients remains an area of ongoing research and debate. The interplay between cancer-related bone loss and the actions and potential benefits of anti-osteoporosis drugs is complex. The plausible biological mechanisms underlying the observed benefits of anti-osteoporosis drugs in cancer patients with osteoporotic fractures warrant exploration. Beyond their direct effects on bone density, these medications may influence the tumour microenvironment, immune response, and the release of factors that affect cancer progression.^{1,3}

The quest for effective interventions to mitigate the profound morbidity and increased mortality associated with the increased susceptibility to fractures in cancer patients has resulted in a plethora of studies exploring the possible beneficial effect of anti-osteoporosis medications in this situation.^{4,7} However, extant literature reveals a heterogeneous admixture of findings. Some studies suggest a potential survival benefit associated with the use of these medications, pointing to their role in preventing further skeletal complications and enhancing overall quality of life while others have failed to demonstrate a significant reduction in mortality.⁴⁻⁷ The interpretation of existing evidence

is complicated by various methodological challenges. Retrospective study designs, heterogeneity in patient populations, varying cancer types and stages, and differences in treatment regimens contribute to the inconsistency in results. The studies have also been limited by biases, including immortal time, healthy user, healthy adherer and unmeasured variable bias. Moreover, the duration of follow-up and the specific anti-osteoporosis drug used can impact the observed outcomes. These methodological limitations underscore the need for well-designed studies with larger sample sizes to draw more definitive conclusions. It is in this context that the paper by Huang CF et al.⁸ in this issue of the Annals has special relevance. The finding in this study that overall survival was considerably higher in both those with and without cancer who were undergoing osteoporosis therapy carries weight because the study used a big data approach and propensity score matching to compare mortality rates between patients who were treated with osteoporosis medication, with those who were not treated. Although there are unknown confounders that the propensity score matching and regression analysis employed in the study could not overcome, the large effect size of the hazard ratio is encouraging. This paper serves as a catalyst for further work in this area.

However, the continued scepticism among clinicians and the uncertainties surrounding the mortality benefits of anti-osteoporosis drugs in cancer patients highlight the need for ongoing research and a critical examination of existing data. Large-scale, multicentre trials that include diverse cancer populations and that utilise standardised methodologies are essential to provide more conclusive evidence. Bridging the gaps in our understanding will facilitate informed clinical decision-making and contribute to improved patient outcomes. Understanding the intricate interactions between cancer cells and bone, the mechanistic impact of anti-osteoporosis medications on senescence as well as cancer

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is crucial for unravelling the true impact of anti-osteoporosis drugs on mortality in this specific patient population.

The heterogeneity of cancer patients calls for an individualised approach to treatment decisions. Factors such as cancer type, stage, prognosis, and the overall health of the patient should be considered when determining the appropriateness of anti-osteoporosis drug therapy. A personalised medicine approach ensures that interventions are tailored to the specific needs and risks of each patient, potentially optimising both skeletal health, cancer progression as well as improving overall survival.

Despite the current uncertainties, the potential impact of anti-osteoporosis drugs on mortality in cancer patients with osteoporosis has significant clinical implications. If robust evidence supports a survival benefit, integrating these medications into the comprehensive care of cancer patients becomes imperative. Conversely, if the evidence remains inconclusive or negative, alternative strategies, such as optimising cancer treatment modalities or exploring novel therapeutic interventions, should be explored.

Keywords: cancer, elderly, mortality, osteoporosis, osteoporotic vertebral fracture

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