Bone Disease in Myeloma: The Claws of CRAB
Rafael Fonseca and Tania Jain

A dynamic approach to use bisphosphonates according to biomarkers of bone metabolism is presented in the Z-MARK study by Raje and colleagues. This is a major step forward toward a rational approach to bisphosphonate usage. Clin Cancer Res; 22(6); 1301-3. ©2016 AACR.

See related article by Raje et al., p. 1378

Multiple myeloma is characterized by the proliferation of monoclonal plasma cells with attendant destruction of bone. The clinical consequences include osteoporosis, lytic bone lesions, and bone destruction. Ultimately, this leads to pathologic fractures and vertebral compressions. The consequences of multiple myeloma bone disease are devastating and include lifelong pain (such as with vertebral compression fractures), disability, and serious decrements of patients’ quality and quantity of life. Randomized studies performed in a time of less effective multiple myeloma therapies showed that the addition of bisphosphonates to standard therapy prevented emergence of skeletal-related events (SRE; refs. 1, 2). It was fortunate that such studies were conducted prior to the advent of more effective anti-multiple myeloma therapies, as in the current era, although SREs after diagnosis are still important, the rate of new fractures is low (3). Hence, achieving clinical trial endpoints could have been more complicated, perhaps to the point of preventing such drugs from being approved if they were developed today. One recent trial, the MRC-IX, showed decreased skeletal events associated with zoledronate over clodronate and improved survival irrespective of bone disease (4). Whether bisphosphonates have any anti-multiple myeloma activity remains disputed.

In this issue of Clinical Cancer Research, Raje and colleagues present a smarter and dynamic approach for bisphosphonate usage (5). Current guidelines recommend the use of bisphosphonates for two years, after which discontinuation or increasing interval between administrations is recommended (6–8). Original recommendations were general “blanket” failing to incorporate adjustments for degree of bone disease, response to therapy, and use of bone metabolism biomarkers or any other biomarkers informing on the appropriateness of therapy. In short, the recommendations are agnostic to the possibility that in selected cases bisphosphonates may not be needed as much, whereas in some cases they should be used for longer. The logic behind this principle is an anachronism and disregards modern opportunities for the adaptation of therapies. Raje and colleagues challenge this by designing a clinical trial that questions whether monthly administration of bisphosphonates is needed in patients with evidence of normal bone metabolism; measured by the urine 115 N-telopeptide of type I collagen (uNTX). This is important as long-term administration of bisphosphonates has been associated with mandible osteonecrosis (9). Mandible osteonecrosis is an avascular bone necrosis with superimposed infection secondary to decreased blood supply. It only happens in the lower mandible, given the low ratio of cortical to spongiform bone, in which alterations of bone formation favoring anabolism can lead to decreased blood supply and necrosis. After all, such ratio of cortical/spongiform bone is essential in a bone that is evolutionarily designed for chewing, hunting, and fighting. If the hypothesis of Raje and colleagues is correct, then bisphosphonates can be administered every 12 weeks, not only diminishing inconvenience but also reducing the risk of mandible osteonecrosis. The study concludes that based on these surrogate markers, less frequent administration of zoledronic acid is associated with a low rate of SREs. It should be noted that the study is quite limited in that it is composed of only a small sample size and therefore the rate of SREs is low. Accordingly, the power to detect differences is limited. However, a formal statistical analysis for such a dynamic approach is difficult, and extrapolation and comparison to other series is appropriate.

Multiple myeloma is the human cancer with best biomarkers. The presence of monoclonal proteins and the various tests available for their testing has no parallel in other cancers. The monoclonal proteins can be detected by simple serum and urine assays, are quantifiable, and can be used for diagnosis as well as monitoring for response and relapse. They are not only disease specific, but patient specific and even clone specific (in the case of biclonal gammopathies). One such marker, the serum-free light chain assay, can accurately predict the risk of renal disease in multiple myeloma patients; in cases without a level of at least 100 mg/dL, the risk of renal damage is low (10). Unfortunately, no such markers exist yet to ascertain the risk of bone disease (8). Such an assay would be of major help in managing benign disease and in monitoring after treatment. Various bone metabolism markers have been used, but without much success. In this study, Raje and colleagues propose the use of uNTX as one of the most elegant examples of using a novel biomarker to measure the need for bone-protecting agents. Other biomarkers for bone metabolism are being developed. Our group is developing an assay of naturally occurring inorganic calcium isotopes as a way to measure in real time whether bone is being formed or destroyed (11). Measuring the various isotope concentrations in blood allows discrimination of patients with multiple myeloma versus...
monoclonal gammopathy of undetermined significance and correlates with bone disease. This is based on the principle that in bone formation, osteoblasts have a slight preference for lighter isotopic versions of calcium. Further development is underway.

What to do clinically then? Bisphosphonates will no longer be developed by the private sector, given two generic alternatives exist, pamidronate and zoledronate. Accordingly, it is unlikely, unless cooperative groups prioritize these trials, that randomized phase III data will exist to guide better the use of this class of drugs. Thus, in patients with controlled multiple myeloma (i.e., those in a stringent complete response) or with no overt bone disease, it is unlikely that much benefit will come from prolonged administration of bisphosphonates. In patients with limited bone disease, it seems likely that effective anti-multiple myeloma therapy with bisphosphonates administered every 12 weeks will be sufficient for most, based on the data of Raje and colleagues. In cases with extreme bone destruction, administration based on the current recommendations seems appropriate. What role will bone biomarkers play is still to be defined. Larger observations studies that incorporate such biomarkers and some of the aforementioned novel ones are needed to have a better estimate of the likelihood of SRE, considering baseline bone status, effectiveness of disease control, and levels of such biomarkers. Extrapolation of this information will likely lead to a better risk-adapted approach use of bisphosphonates.

Finally, in myeloma, four events are the predominant determinants of progression for the benign state to the cancer form of the disease (other new criteria recently added; ref. 12). These are hypercalcemia, renal insufficiency, anemia, and the presence of bone disease, best remembered by the mnemonic of CRAB (Fig. 1). Although anemia and hypercalcemia can be serious, they are largely reversible and without major long-term consequences (the CRAB legs). In stark contrast, development of renal failure or bone complications can seriously hamper patients’ quality of life and also limits patients’ life expectancy. Those are the most dangerous complications of myeloma; the CRAB claws! The study by Raje and colleagues hits the “mark”, suggesting smarter ways of managing bisphosphonates.

Disclosure of Potential Conflicts of Interest

R. Fonseca reports receiving royalties, through his institution, from Abbott Diagnostics for intellectual property on FISH probes used to prognosticate multiple myeloma based on genetic categorization of the disease, which is owned by Mayo Clinic and licensed to Abbott Diagnostics; is a consultant/advisory board member for Amgen, Applied Biosciences, Bayer, Bristol-Myers Squibb, Celgene, Janssen, Millennium Pharmaceuticals, Novartis, and Sanofi-Aventis; and is listed as a co-inventor on a pending patent application, which is owned by Arizona State University, for the use of calcium isotopes as biomarkers of bone metabolism. No potential conflicts of interest were disclosed by the other author.

Authors’ Contributions

Conception and design: R. Fonseca
Writing, review, and/or revision of the manuscript: R. Fonseca, T. Jain
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R. Fonseca

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