CORR Insights

CORR Insights®: Do Long Term Survivors of Ewing Family of Tumors Experience Low Bone Mineral Density and Increased Fracture Risk?

Timothy A. Damron MD

Where Are We Now?

Hobusch and colleagues presented the largest series to date of survivors of Ewing family of tumors who have been evaluated for bone-mineral density (BMD) and fractures. Most of the earlier series

evaluating BMD merged the Ewing patients and often overshadowed them with osteosarcoma and/or other solid tumors [7, 9]. The overall BMD findings by Hobusch et al. are not surprising, showing that there is a relatively high prevalence (31 of 56; 56%) of pathologic bone density in this patient population. Their clinical fracture occurrence is also relatively high, showing that 29 fractures occurred in 22 of 56 patients. However, perhaps the most interesting fact was that while osteopenia/osteoporosis and fractures were frequent, the two did not seem to be related. This may be the result of a beta error ... or perhaps not.

The possibility of osteopenia/osteoporosis failing to explain the fractures is particularly interesting considering that in a similar related situation – postradiation bone, as seen in the treatment of soft tissue sarcoma – fractures also occur with increased

frequency compared to controls, but without any apparent decrease in BMD [4]. Preliminary evidence in those patients similarly suggests increased bone fragility independent of bone density. In 2011, Dhakal et al. [4] reported as similar disconnect between BMD and fracture among 19 patients status post surgical excision and radiotherapy treatment for soft tissue extremity sarcomas. Despite knowing that patients who undergo radiotherapy treatment for extremity soft tissue sarcomas have been widely recognized to have an increased risk of fracture, the mean BMD at all irradiated sites in these 19 patients was, on average, higher than the contralateral anatomic site. In the current study, nine of 36 patients who received radiotherapy had fractures in the radiation field. Other studies [3, 5] have shown higher rates of fracture for irradiated femurs in patients with Ewing family of tumors. However, in the current study, the rate was only 40%. The fact that the majority of the fractures occurred outside the irradiated field and in patients who did not have pathologic bone density remains an enigma.

This CORR Insights® is a commentary on the article “Do Long Term Survivors of Ewing Family of Tumors Experience Low Bone Mineral Density and Increased Fracture Risk? by Hobusch and colleagues available at: DOI: 10.1007/s11999-014-3777-5.

The author certifies that he, or any members of his immediate family, have no funding or commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research®* editors and board members are on file with the publication and can be viewed on request.

The opinions expressed are those of the writers, and do not reflect the opinion or policy of *CORR®* or the Association of Bone and Joint Surgeons®.

This *CORR Insights®* comment refers to the article available at DOI: 10.1007/s11999-014-3777-5.

T. A. Damron MD (✉)
David G. Murray Professor of
Orthopaedics, Institute for Human
Performance, Musculoskeletal Science
Research Center, 505 Irving Avenue,
Room 3117, Syracuse, NY 13210, USA
e-mail: damront@upstate.edu

CORR Insights

Therefore, what we know now is (1) pediatric patients who receive chemotherapy treatment for Ewing family of tumors, just like those treated as children for osteosarcoma and other childhood tumors (leukemia, lymphoma), are very likely to have low BMD entering adulthood, and (2) those same patients are more likely than their cohorts to have fractures. What we do not know is what other factors may be in play beyond BMD density alone, since the pathologic BMD may not account for all of the fractures.

Where Do We Need To Go?

As the authors note, “If BMD changes cannot explain the propensity of fractures, there may be other bone characteristics like microarchitectural changes of bone to more accurately explain the effect.” Factors other than BMD likely contribute to the occurrence of these fractures, both following chemotherapy and radiotherapy, and those factors may include biological, biomechanical, and biochemical changes. Those factors require further investigation. A fair amount of work has been done on the biologic effects of both chemotherapy and radiotherapy on osteoblasts and osteoclasts with the common theme being an uncoupling of osteoclastic resorption and

osteoblastic bone formation leading to abnormal bone formation at least temporarily following chemotherapy and sometimes permanently following radiotherapy. Our own biomechanical evaluation of irradiated bone [10] has shown that diminished bone content and resultant structural properties of the remaining bone fail to explain the biomechanical weakening of the bone. Hence, we are left with biochemical changes, which is where the answer may lie.

How Do We Get There?

As suggested by the current authors, there are two routes that are worth exploring. The first is to evaluate larger numbers of patients prospectively in order to determine whether this disconnect between BMD and fracture is real or a statistical anomaly. The second is to evaluate other potential contributing factors to explain the disconnect, and, as noted above, the biochemical changes would appear to be a promising target. At least for radiotherapy, there appear to be intrinsic biochemical changes within the remaining bone that are candidates to explain the fragility. Radiation-induced biochemical changes – including altered collagen crosslinking, crystallinity, and mineral-to-matrix ratio as well as an increase in

advanced glycation end products – may ultimately prove to account for the increased fragility [1, 2, 6, 8]. The same kinds of changes have yet to be investigated for bone treated by chemotherapeutic agents such as those used for pediatric patients with sarcomas, including Ewing family of tumors, and other solid tumors. Therefore, more work lies ahead in this area, and the current article provides an impetus for it.

References

1. Açil Y, Gierloff M, Behrens C, Möller B, Gassling V, Niehoff P, Wiltfang J, Simon M. 2013 Effects of zoledronate on irradiated bone in vivo: Analysis of the collagen types I, V and their cross-links lysylpyridinoline, hydroxyllysylpyridinoline and hydroxyproline. *Calcif Tissue Int.* 92:251–260.
2. Açil Y, Springer IN, Niehoff P, Gassling V, Warnke PH, Açmaz S, Sönmez TT, Kimmig B, Lefteris V, Wiltfang J. Proof of direct radiogenic destruction of collagen in vitro. *Strahlenther Onkol.* 2007;183:374–379.
3. Damron TA, Sim FH, O'Connor MI, Pritchard DJ, Smithson WA. Ewing's sarcoma of the proximal femur. *Clin Orthop Relat Res.* 1996;322:232–244.
4. Dhakal S, Chen J, McCance S, Rosier R, O'Keefe R, Constine LS. Bone density changes after radiation for extremity sarcomas: Exploring

CORR Insights

- the etiology of pathologic fractures. *Int J Radiat Oncol Biol Phys.* 2011;80:1158–1163.
5. Fuchs B, Valenzuela RG, Sim FH. Pathologic fracture as a complication in the treatment of Ewing's sarcoma. *Clin Orthop Relat Res.* 2003;25–30.
 6. Gong B, Oest ME, Mann KA, Damron TA, Morris MD. 2013 Raman spectroscopy demonstrates prolonged alteration of bone chemical composition following extremity localized irradiation. *Bone.* 57:252–258.
 7. Kaste SC, Ahn H, Liu T, Liu W, Krasin MJ, Hudson MM, Spunt SL. Bone mineral density deficits in pediatric patients treated for sarcoma. *Pediatr Blood Cancer.* 2008 May;50:1032–1038.
 8. Oest ME, Damron TA. Focal therapeutic irradiation induces an early transient increase in bone glycation. *Radiat Res.* 2014;181:439–443.
 9. Pirker-Frühauf UM, Friesenbichler J, Urban EC, Obermayer-Pietsch B, Leithner A. Osteoporosis in children and young adults: a late effect after chemotherapy for bone sarcoma. *Clin Orthop Relat Res.* 2012;470:2874–2885.
 10. Wernle JD, Damron TA, Allen MJ, Mann KA. 2010 Local irradiation alters bone morphology and increases bone fragility in a mouse model. *J Biomech.* 43:2738–2746.