

Vertebral compression fractures during chemotherapy for childhood acute lymphoblastic leukemia: commentary on a report from the STeroid Associated Osteoporosis in the Pediatric Population (STOPP) research program

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Submitted Aug 19, 2012. Accepted for publication Sep 25, 2012.

doi: 10.3978/j.issn.2224-4336.2012.09.04

View this article at: <http://www.thetp.org/article/view/1089/1396>

Children diagnosed with acute lymphoblastic leukemia (ALL) can present with vertebral fractures at diagnosis, or may develop vertebral fractures during treatment for their disease. In a recent manuscript published in the *Journal of Clinical Oncology*, Alos *et al.* (1), reported incident vertebral fractures 12 months from diagnosis among 25 of 155 (16%, 95% CI: 11-23%) children. Vertebral fractures were detected and graded by applying Genant semiquantitative methodology to lateral thoracolumbar radiographs, and were associated with prevalent vertebral fractures at diagnosis (OR 7.3, 95% CI: 2.3-23.1) and low bone mineral density (OR 1.8, 95% CI: 1.2-2.7 for a one standard deviation reduction in BMD). Grade of fracture at diagnosis was also associated with incident fracture at 12 months. Among children with no vertebral fracture, only back pain reported after diagnosis was associated with incident vertebral fracture. Children with incident vertebral fracture did not differ from those without fracture by age, sex, anthropometric characteristics, methotrexate or glucocorticoid exposure, leukemia immunophenotype, white blood cell count, physical activity, bone age, or calcium or vitamin D intake.

The main findings in this study are consistent with previously reported data from adult cohorts describing bone mineral density and associated fracture risk (2). As the authors pointed out, low BMD in adults is associated with fracture risk, and an initial vertebral fracture in postmenopausal women is associated with a five-fold increased

risk for an additional fracture 12 months later (3). The results of this study, however, do differ in at least one important way from studies done in older adult populations: children with incident fracture had larger gains in BMD over the course of the 12 month treatment period than children without fracture, indicating that an injury response may be present in these children during treatment for ALL, despite fairly continuous suppression of their innate immune response. This finding has not been reported in adult populations (4). Interpretation of this finding should, however, take into account a limitation of dual x-ray absorptiometry measurement of BMD. That is, when compression fractures are included in the assessed skeleton, BMD will be increased due to compression of undermineralized bone, leading to an artificial increase in measured BMD (5). A solution to this problem is to use quantitative computerized tomography measurement of spinal BMD, excluding those vertebrae with fracture from the estimate (6).

The failure of this study to detect an association between disease characteristics, treatment exposure and fracture risk is not surprising because of the homogeneity of the study population and the small sample size. There was likely not enough variability in the chemotherapy exposures to detect the independent effects of these agents on bone. It is also possible that vertebral fracture during the first 12 months of treatment for ALL is related to chemotherapy exposure or dose in some children, but not in others, because of inherent differences in the ways that they metabolize these

chemotherapy agents. The authors describe a possible effect of sensitivity to glucocorticoids given the observation of a more pronounced increase in BMI over 12 months in individuals who experienced *de novo* incidental vertebral fracture, when compared to others. Previous studies have identified associations between folate-related and vitamin D-receptor genetic variants and low bone mineral density in children with ALL (7,8). The authors also discuss the possibility that disease related bone damage, or leukemic cell activation of osteoclast stimulating factors (9), may differ from the treatment related bone damage that has previously been described in the childhood ALL survivor population (10). In a recent study by Rayar *et al.* (11), the association between dexamethasone and fractures in children with ALL was shown to become significant only 40 weeks after diagnosis. These findings indicate that later fractures may be more specifically related the exposure to chemotherapy while early fractures may be more associated with the primary disease itself.

The authors have identified those children at greatest risk for incident fracture 12 months after beginning therapy. Unfortunately, at this time, there are no proven interventions to either prevent or remediate this problem. Symptom management is available for pain (12). Activity restrictions are often recommended, although there is little evidence to indicate that this will actually prevent worsening of existing fracture or onset of new fracture. It is possible that some sort of a physical activity intervention may prevent fracture by stimulating positive bone remodeling even during treatment. Recent literature indicates that jumping or strengthening type activities at an intensity of 10 minutes per day is required to improve bone mineral density among children without active disease (13). This may be difficult for children with ALL to do while receiving chemotherapy agents with toxicities that include proximal muscle weakness and peripheral neuropathy, which may be superimposed upon pain from fractures.

A key clinical question raised by Alos *et al.* (1) is whether or not children with ALL presenting with vertebral fracture at diagnosis should be treated with pharmacological agents such as bisphosphonates. There have been no randomized, placebo-controlled clinical trials of these agents in children with ALL, although one series of two patients with fracture reported success when Pamidronate was administered with Vitamin D and calcium supplementation (14). Two other non-randomized trials gave alendronate and calcium supplementation or pamidronate to small groups of children with low BMD (15,16) during treatment for ALL

or NHL and reported improved BMD and radiographic findings with no short term adverse events. The potential interactions between bisphosphonates and chemotherapy agents as well as the long-term effects of bisphosphonate therapy in children with ALL remain unknown. These agents do have, however known side-effects which require caution in using them in this vulnerable population (17). Furthermore, the impact of incident vertebral fractures and low BMD observed within the first few years following the completion of cancer therapies on the long-term bone health of childhood cancer survivors remain unknown.

A recent report from the Childhood Cancer Survivor Study indicates that fractures in adult survivors of childhood cancer are not more common than those observed among their siblings (18). In addition, Van Staa *et al.* (19) indicate that BMD improves rapidly following discontinuation of glucocorticoid therapy in children. Children with ALL, treated on modern protocols, do demonstrate some degree on bone recovery after treatment ends (20). Interventions early in survivorship for those survivors who have persistent impairment may hold more promise for bone health than adding additional medication burden during the already intense treatment phases of ALL therapy.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Alos N, Grant RM, Ramsay T, et al. High incidence of vertebral fractures in children with acute lymphoblastic leukemia 12 months after the initiation of therapy. *J Clin Oncol* 2012;30:2760-7.
2. Gehlbach S, Saag KG, Adachi JD, et al. Previous fractures at multiple sites increase the risk for subsequent fractures: the Global Longitudinal Study of Osteoporosis in Women. *J Bone Miner Res* 2012;27:645-53.
3. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001;285:320-3.
4. Delmas PD, Seeman E. Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral

- fracture risk with anti-resorptive therapy. *Bone* 2004;34:599-604.
5. Paiva LC, Filardi S, Pinto-Neto AM, et al. Impact of degenerative radiographic abnormalities and vertebral fractures on spinal bone density of women with osteoporosis. *Sao Paulo Med J* 2002;120:9-12.
 6. Adams JE. Quantitative computed tomography. *Eur J Radiol* 2009;71:415-24.
 7. Relling MV, Yang W, Das S, et al. Pharmacogenetic risk factors for osteonecrosis of the hip among children with leukemia. *J Clin Oncol* 2004;22:3930-6.
 8. te Winkel ML, de Muinck Keizer-Schrama SM, de Jonge R, et al. Germline variation in the MTHFR and MTRR genes determines the nadir of bone density in pediatric acute lymphoblastic leukemia: a prospective study. *Bone* 2011;48:571-7.
 9. Jayanthan A, Miettunen PM, Incoronato A, et al. Childhood acute lymphoblastic leukemia (ALL) presenting with severe osteolysis: a model to study leukemia-bone interactions and potential targeted therapeutics. *Pediatr Hematol Oncol* 2010;27:212-27.
 10. Wasilewski-Masker K, Kaste SC, Hudson MM, et al. Bone mineral density deficits in survivors of childhood cancer: long-term follow-up guidelines and review of the literature. *Pediatrics* 2008;121:e705-13.
 11. Rayar MS, Nayiager T, Webber CE, et al. Predictors of bony morbidity in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2012;59:77-82.
 12. Van Cleve L, Bossert E, Beecroft P, et al. The pain experience of children with leukemia during the first year after diagnosis. *Nurs Res* 2004;53:1-10.
 13. Meyer U, Romann M, Zahner L, et al. Effect of a general school-based physical activity intervention on bone mineral content and density: a cluster-randomized controlled trial. *Bone* 2011;48:792-7.
 14. Goldbloom EB, Cummings EA, Yhap M. Osteoporosis at presentation of childhood ALL: management with pamidronate. *Pediatr Hematol Oncol* 2005;22:543-50.
 15. Lethaby C, Wiernikowski J, Sala A, et al. Bisphosphonate therapy for reduced bone mineral density during treatment of acute lymphoblastic leukemia in childhood and adolescence: a report of preliminary experience. *J Pediatr Hematol Oncol* 2007;29:613-6.
 16. Wiernikowski JT, Barr RD, Webber C, et al. Alendronate for steroid-induced osteopenia in children with acute lymphoblastic leukaemia or non-Hodgkin's lymphoma: results of a pilot study. *J Oncol Pharm Pract* 2005;11:51-6.
 17. Prommer EE. Toxicity of bisphosphonates. *J Palliat Med* 2009;12:1061-5.
 18. Wilson CL, Dilley K, Ness KK, et al. Fractures among long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer* 2012;118:5920-8.
 19. van Staa TP, Cooper C, Leufkens HG, et al. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res* 2003;18:913-8.
 20. Kadan-Lottick N, Marshall JA, Barón AE, et al. Normal bone mineral density after treatment for childhood acute lymphoblastic leukemia diagnosed between 1991 and 1998. *J Pediatr* 2001;138:898-904.

Cite this article as: Ness KK, Chemaitilly W, Kaste SC. Vertebral compression fractures during chemotherapy for childhood acute lymphoblastic leukemia: commentary on a report from the STeroid Associated Osteoporosis in the Pediatric Population (STOPP) research program. *Transl Pediatr* 2012;1(2):65-67. doi: 10.3978/j.issn.2224-4336.2012.09.04