

Dilemma's regarding vertebral fractures in children with acute lymphoblastic leukemia (ALL)

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Acute lymphoblastic leukemia (ALL) is the most frequently occurring type of cancer in children, which currently, due to optimized stratification and treatment regimens, has become curable in 80-90% of all cases (1). The increasing number of long term survivors has resulted in gain of knowledge and increased awareness of complications that may already occur during treatment as well as later in life. Osteoporosis, a disorder that is characterized by low bone mineral density (BMD) and consequent increased susceptibility of fractures (2), has been shown to occur already during ALL treatment, which in all cases at least includes corticosteroids and methotrexate (MTX) (3-5). In the 2012, July 18th issue of the *Journal of Clinical Oncology*, Alos *et al.* (6) reported for the first time a high frequency of baseline and treatment-related vertebral fractures in pediatric ALL patients. Twenty-five (16%) of the 155 children had one or more incident vertebral fractures within twelve months after the initiation of therapy. More than 50% of the children with incident vertebral fractures, presented with fractures before starting therapy. Fracture risk was highly associated with low lumbar spine BMD at baseline, but not with change in BMD from baseline to 12 month of follow-up, as measured by dual X-ray absorptiometry (DXA). This underscores our earlier findings that genetic variation in bone mass, which seems to determine lower baseline BMD and fracture risk, rather than treatment-related decline of bone mass in pediatric ALL, is important for the development of vertebral fractures (7,8). In this study, it is unclear, whether the fracture rate is more determined by the leukemia (baseline associated BMD) or the antileukemic treatment (BMD at

12 months), as these data are not separately issued in the manuscript.

Retrospective studies in children with ALL have shown associations between steroid treatment and low BMD (3-5). Alos *et al.* (6) did not find an association between the total cumulative dose of glucocorticoids, nor methotrexate and incident vertebral fractures. This may indicate that intensity of treatment is not the most important determinant of fracture risk. As the fracture rate seems to be also high in the normal age-matched Canadian population, it may be that genetic factors, which may also denominate BMD at presentation (7,8), play a more prominent role, especially in this ethnic Canadian population. Alternatively, environmental factors may be of importance. Unfortunately, other than treatment-related potential risk factors, data on calcium and vitamin D supplements, hours of sunshine or physical activity measurements in association with incident vertebral fractures were not included in the analyses in the current study.

Interpreting measurements of bone mineral density of the lumbar spine in growing children is challenging, especially in case of treatment with multi-agent therapy and/or radiotherapy. For that reason, correction of BMD for height, by measurement of B(M)AD, is an accurate measure of bone mineral density (9). These data were unfortunately not available in the indicated manuscript. The other challenge is the interpretation of bone mineral density of the lumbar spine, in case of a fracture in the region of interest by DXA scan. Finally, there can be considerable variation in results of DXA scans and control groups as measured per center for which calibration is warranted in

multicenter studies .

These issues may be the reason that, although fractures are the major clinical manifestation of osteoporosis, only few previous studies on vertebral fracture risk in children treated for ALL have been performed. Recently, in a large prospective study among almost 700 children treated for ALL, we observed that the cumulative incidence of clinically symptomatic vertebral fractures was comparable (personal communication, manuscript submitted) to the incidence of severe vertebral fractures (five of 155 children; 3.1%) that was reported in the current study. It is conceivable, that the total estimated incidence of vertebral fractures of 16% in the current study sample could have been an over- or underestimation of the “real” incidence of vertebral fractures in the ALL population, as illustrated by the spread in the confidence interval (11% to 23%). Moreover, since only less than half of the eligible children (only 155/368 ALL cases) were included, at least some selection bias may have influenced the results. In fact, getting insight in the excess incidence of vertebral fractures in children with ALL is only possible when compared with a national-based aged-matched healthy control cohort. To our knowledge, no studies in ALL have been performed as compared to healthy children in which the incidence of vertebral fractures was assessed prospectively, using lateral radiographs of the lumbar spine and DXA scan concomitantly. Nevertheless, recently, in a prospective study, the STOPP consortium, which performed the hereby reported study, reported an incidence of 6% incident vertebral fractures among children with rheumatic disorders one year after initiation of glucocorticoid therapy (10). This is less than twice the risk among the currently reported children treated for ALL, and this may indicate that the fracture risk in children with ALL indeed is substantial.

All these issues together illustrate the difficulties to accurately assess the incidence of vertebral fractures in children with ALL, and further prospective larger cohort studies that harmonize vertebral fracture definitions and methods are needed. Currently, there is no gold standard for defining prevalent and incident vertebral fractures and therefore, frequencies depend up on the used methods and criteria. In the current study, the semi-quantitative method of Genant was used, which is reliable when used by expert clinicians who are trained to discriminate between anatomical variants and technical artifacts on the photographs (11,12).

The authors point to the major question whether interventions, such as administration of bisphosphonates,

should be considered in children with ALL, to prevent fractures. Before justifying the use of such agents in children with ALL, several issues need to be considered. In adults, bisphosphonates show several side effects, and up until now, safety and efficacy studies using these agents in children treated for ALL are not available. In children with osteogenesis imperfecta, oral bisphosphonate therapy was well tolerated and effectively reduced the risk of fractures (13). Secondly, to date, it is not clear how subgroups of children with ALL with an increased fracture risk, which may benefit from intervention, can be identified. For that reason, reliable risk models need to be developed to identify pediatric ALL patients with a high (vertebral) fracture risk. Also, the value of routinely performed diagnostic DXA scans, the relevance of genetic variation and the history of previous fractures should be weighted. Randomized controlled trials are than further necessary to assess whether treatment with bisphosphonates in high (fracture-) risk patients is effective in reducing the number of future fractures to prevent invalidity in future (adult) life. Finally, information on late sequelae after vertebral fractured pediatric ALL patients during therapy, needs to be addressed in future studies.

In conclusion, Alos *et al.* stress the importance of awareness of vertebral fractures that are present before starting treatment, which apparently may have been disguised previously in childhood ALL. Further large scale studies are necessary to identify risk profiles and to develop interventions to prevent serious fractures and consequent future late sequelae in pediatric ALL patients at high risk.

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Footnote

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

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