



Hyundai Hope on Wheels Hyundai Scholar Research

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As the number of pediatric cancer survivors grows, clinical research directed toward understanding and mitigating the acute toxicities and late-effects of cancer treatment becomes increasingly important. There are estimated to be 270,000 survivors of childhood cancer nationwide.¹ Over 80% of childhood acute lymphoblastic leukemia (ALL) patients are expected to become long-term event-free survivors.² While the successes in the treatment of childhood cancers are impressive, treatments remain non-specific and associated toxicities can be life-altering. Continued attention to decreasing the toxicity of treatment, both during therapy and with regard to chronic morbidities, is essential if we are to improve the quality of life of childhood cancer survivors.

Skeletal toxicity has emerged as an important complication of therapy for childhood ALL. Increased rates of fracture and osteonecrosis have been noted in multiple patient cohorts. For example, a retrospective study of children with ALL treated at the Dana-Farber Cancer Institute (DFCI) demonstrated a 5-year cumulative fracture incidence of 28%, with median time from diagnosis of ALL to first fracture of 15 months, as well as a 5 year-cumulative incidence of osteonecrosis of 7%.³ While skeletal morbidity has been increasingly recognized as a major treatment-related toxicity of childhood ALL therapy, much remains to be elucidated about risk factors, long-term outcomes, the role of screening, proper management, and potential preventative and interventional strategies. Bone mass attained early in life is considered a major determinant of long-term bone health. A detailed understanding of how bone changes during and after leukemia therapy is needed in order to identify those at greatest risk of toxicity and to develop effective interventions that prevent significant morbidity and promote long-term bone health.

We plan a prospective, longitudinal assessment of bone mineral density in children with ALL, utilizing peripheral quantitative computed tomography (pQCT), a modality with advantages over standard bone mineral content measurement techniques. Through use of pQCT, we hope to gain a detailed understanding of how bone mineral status and bony architecture changes over time in children during and after leukemia therapy. In exploratory analyses, we will examine the relationship between pQCT findings and risk of fracture and osteonecrosis, and between pQCT findings and 25-hydroxy vitamin D level. Vitamin D

deficiency has been recognized as an important concern with regard to bone health, even for healthy children, emphasized by the recent American Academy of Pediatrics recommendation for increased minimal daily vitamin D intake. While children undergoing leukemia treatment may be at risk for vitamin D deficiency, the impact of vitamin D status with regard to acute and long-term skeletal morbidities has not been thoroughly explored in this population.

This research project is fostered through a unique collaboration between the Dana-Farber Cancer Institute-Acute Lymphoblastic Leukemia Consortium, the David B. Perini, Jr. Quality of Life Clinic for childhood cancer survivors, and the Children's Hospital Boston Bone Health Program. We intend for this study to inform future screening efforts aimed at identifying ALL patients with the greatest risk of skeletal toxicity as well as the development of effective interventions to protect bone health and decrease the incidence of skeletal toxicities.

In addition to the initiation of the project detailed above, we will continue several analyses. For example, we are conducting a retrospective review of the incidence of and risk factors for skeletal toxicity in patients with history of underlying hematologic malignancy treated with allogeneic hematopoietic stem cell transplantation (HSCT) over a 6-year period at Dana-Farber Cancer Institute and Children's Hospital Boston. We anticipate that this analysis will inform further screening and interventional studies aimed at decreasing post-HSCT skeletal morbidity. In addition, we are conducting an analysis investigating long-term outcomes after childhood cancer in infancy. When faced with caring for survivors of childhood cancer treated at very young age, there is little reported that focuses in detail on this potentially vulnerable group. The Childhood Cancer Survivor Study (CCSS) was established as a resource for investigating the long-term outcomes of a cohort of 5-year survivors of childhood cancer, diagnosed from 1970-1986. We will assess long-term health status and chronic medical conditions in those diagnosed with malignancy in infancy.

With the support of the Hyundai Scholars grant, I will continue to develop my research efforts in childhood cancer survivorship, with a focus on skeletal toxicities in hematologic malignancy. The Hyundai Scholars Program would provide funding essential for initiating and completing the projects above. The Hyundai funds would be used for salary support and research materials during the period of the award.

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3. Strauss AJ, Su JT, Dalton VM, Gelber RD, Sallan SE, Silverman LB. Bony morbidity in children treated for acute lymphoblastic leukemia. *J Clin Oncol*. 2001;19:3066-3072.