Marrow Cell Transplantation For Infantile Hypophosphatasia.

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Hypophosphatasia seems to be an ideal model for assessing marrow or stem cell transplantation for osteopathies, like osteogenesis imperfecta, involving defects intrinsic to osteoblasts. In this inborn error of metabolism, a variety of parameters can be readily followed to judge efficacy. Hypophosphatasia is characterized by deficient activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP) causing hypophosphatasemia. Additionally, three phosphocompounds (putative TNSALP substrates) accumulate endogenously and can be quantitated in plasma or in urine [phosphoethanolamine (PEA), inorganic pyrophosphate (PPi), and pyridoxal 5/-phosphate (PLP)]. Finally, there is skeletal disease due to defective mineralization of cartilage and bone presenting, depending on patient age, as rickets or as osteomalacia. Disease severity is reflected by ALP, PEA, PPi, and PLP levels. Possibly, extracellular accumulation of PPi, an inhibitor of calcification, explains the skeletal disease. Autosomal recessive inheritance can account for all clinical forms of hypophosphatasia, however, at least 70 different TNSALP gene defects have been identified. There is no established medical treatment.

A 6-month-old girl with infantile hypophosphatasia, often lethal in the first year of life, manifested failure to thrive and progressively worsening rickets after age 2½ months and developed multiple fractures, scoliosis, and other deformities which indicated a lethal outcome. In hopes of providing ALP-replete cells, she underwent bone marrow transplantation (BMT) at age 8 months. Her healthy sister (4/6 HLA antigen matching and genetically identical for DRB1 resulting from a crossover event in the patient) was the donor. After busulfan, cyclophosphamide, and anti-thymocyte globulin preparation, BMT was performed with T-cell depleted mononuclear cells. Graft-vs-host disease (GVHD) prophylaxis consisted of cyclosporine and prednisone.

Transfusion independence occurred rapidly (day +12) after BMT, and without evidence of acute GVHD or subsequent hematopoietic cell rejection. Follow-up skeletal x-rays, first obtained on day +100, demonstrated remarkable reversal of her worsening skeletal disease. There was healing of rachitic defects and generally improved skeletal mineralization. At 4 months after BMT, developmental milestones were regained without additional fractures. There was no evidence of chronic GVHD. Nevertheless, hypophosphatasemia and low serum levels of bone ALP were essentially unchanged, and high levels of plasma PLP and elevated urinary PPi and PEA concentrations also persisted.

At 6 months after BMT, once again there was arrest of developmental milestones with clinical and radiographic evidence of skeletal deterioration, although there was no evidence of BMT rejection (peripheral leukocytes >90% donor). A non T-cell depleted boost with stromal cell expansion from her sister was performed without induction or immunosuppression at age 1½ years and was well tolerated. Soon after, prednisone therapy seemed helpful for respiratory distress during pneumonia and has been continued to date. Radiographs 9 months after the boost once again showed significant improvement that persists now at age 2-3/4 years. The biochemical abnormalities, however, remain essentially unchanged. The patient is small with significant scoliosis, but walks with assistance and has excellent intellectual development and fine motor skills.

In our patient with infantile hypophosphatasia, rescue with clinical and radiographic improvement following BMT (without discernible biochemical change) is consistent with engraftment of small numbers of donor marrow stromal cells producing ALP-replete, functional osteoblasts. Alternatively, ALP-containing hematopoietic cells in marrow spaces could account for the findings. Further, investigation using the TNSALP knock-out mouse and additional appropriate hypophosphatasia patients will be necessary to clarify our preliminary observations.

Reference: Proceedings of the 7th International Conference on Osteogenesis Imperfecta. Montreal, Canada, 1999.