

Stem Cell Therapies for Dysmyelinating Diseases

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Leukodystrophies are a family of diseases that result from defects in lysosomal enzymes (see Chapter 43). Some 40 known lysosomal storage diseases cumulatively affect 1 in 5,000 births. Much of the pathology associated with the disorders is related to the degree of substrate accumulation, as well as the sensitivity of the cell to the stored substrate. A general principle behind stem cell or gene therapies is that successful engraftment will provide a source of the missing enzyme for the life of a patient.

Hematopoietic stem cell transfer (HCT) has been used for several decades to cure or arrest several neurodegenerative lysosomal storage diseases. Disease phenotype and extent of the disease at the time of treatment have proven to be important variables:

- Krabbe disease is caused by a deficiency of galactocerebrosidase, an essential enzyme for myelin metabolism. Results of a very small clinical trial of patients with infantile Krabbe disease found that children who received umbilical cord blood stem cells from unrelated donors prior to symptom onset developed with little neurological impairment. Disease progression stabilized faster in patients who received cord blood compared to those who received adult bone marrow. Bone marrow transplantation has been shown to benefit mild cases early in the course of the disease.
- Cerebral X-linked adrenoleukodystrophy (X-ALD) is a clinically heterogeneous X-linked leukodystrophy affecting fatty acid metabolism. The majority of affected boys also have Addison's disease, and neurological deterioration includes visual, hearing and motor deficits. While HCT is the only potentially effective treatment, it is recommended only when cerebral disease is present. The first HCT for X-ALD was performed in 1982, and long-term HCT results

have been reported. Typically, boys with very early stage disease are the best candidates. Recently, insertion of the corrected gene in autologous hematopoietic stem cells has shown clinical outcomes similar to allogeneic HCT, suggesting that gene therapy of the patient's own stem cells may prove practical.

- Globoid cell leukodystrophy (GLD) is a recessive lysosomal disorder due to deficiency of galactocerebroside GalC. When manifested with early onset, this is classical Krabbe disease, and can lead to death. HCT for GLD was reported in 1998 in five cases, and additional information on umbilical cord transplants is accumulating.
- Metachromatic leukodystrophy (MLD) is a recessive lysosomal storage disorder due to deficiency of arylsulfatase A, and can present at various stages, with the earliest infantile forms leading to death within years. All forms of the disease involve progressive deterioration of motor and neurocognitive function. HCT for MLD has proven challenging, with rather disappointing results for infantile forms due to rapid progression of the disease itself. HCT may be useful in stabilizing CNS disease in late-onset patients, while having little benefit for the PNS components.

Despite significant progress, HCT is still associated with significant risks of graft failure or graft-versus-host-disease, and there is strong interest in identifying optimal treatment variables. Stem cell sources for transplantation are bone marrow, peripheral blood and cord blood. Preparative conditioning with supralethal chemoradiotherapy is needed for donor cell engraftment, and immunosuppressive agents are given for months as prophylaxis against graft-versus-host disease (GVHD).