HHS Public Access

Author manuscript

Regen Med. Author manuscript; available in PMC 2015 May 06.

Published in final edited form as:

Regen Med. 2013 September ; 8(5): 527–529. doi:10.2217/rme.13.46.

Prospects for stem cell therapy in Neuronal Ceroid Lipofuscinosis

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Neuronal ceroid lipofuscinoses (NCL), sometimes collectively referred to as Batten disease, represent a clinically and genetically heterogeneous class of lysosomal storage disease characterized by neurodegeneration in the setting of progressive accumulation of autofluorescent storage material. To date 13 distinct genotypes associated with the NCLs have been identified, with clinical manifestations originating from the perinatal period through adulthood [1]. Despite variations in age of onset, these disorders have common clinical features, including loss of vision, seizures and cognitive decline. Collectively, the NCLs represent the most common neurodegenerative disorders of childhood. Although the natural history of NCL is relentlessly progressive, stem cell-based therapies have recently emerged as a potential therapy for the disease, as evidenced by the results of a recent phase I clinical trial (NCT00337636, [2]). In this clinical trial, 6 children with NCL caused by deficiency of the CLN1 or CLN2 enzymes were given stereotactically-guided injections of fetal human central nervous system stem cells (HuCNS-SC) into each cerebral hemisphere and ventricles. This therapy was well-tolerated. Although substantial functional improvements were not observed, the patients selected for this trial were in the late stages of disease.

In considering the promise and pitfalls of stem cell therapies, it is important to recognize that “Batten disease” is more than one disease. Infantile and late infantile NCL caused by mutations in CLN1 and CLN2, respectively, are associated with soluble enzymes whose activity can be assayed biochemically [3]. In contrast, the function of the integral transmembrane protein CLN3, defects of which cause the juvenile form of NCL (Batten Disease) has remained enigmatic although it is conserved throughout eukaryotic evolution [4].

Enzyme replacement therapy, effective in treating peripheral manifestations of lysosomal storage diseases, does not represent a viable option for the NCLs at the present time given the inherent difficulty in delivering therapies across the blood-brain-barrier. Attempts to circumvent this barrier are underway, for example, using implantable intrathecal pumps [5] and transient osmotic blood-brain-barrier disruption (NCT00983398). In contrast, stem cell

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therapies appear to have shown therapeutic benefit for other severe neurological diseases of childhood, most recently in patients with the hypomyelinating disorder Pelizaeus-Merzbacher disease [6]. In this study, HuCNS-SC were implanted into the deep white matter of the brain of children with a severe form of Pelizaeus-Merzbacher disease. One year open-label assessment showed an improvement in several MRI parameters suggesting *de novo* myelin production, and three out of the four children showed apparent gains in neurological function.

Several institutions have robust stem cell transplant programs (albeit mostly peripheral, not CNS-directed) already in place for inherited neurometabolic diseases. Protocols differ in their approach, using matched related or unrelated donor marrow or umbilical cord blood grafts (NCT00004378; NCT01043640); placental and/or umbilical cord blood-derived cell infusions (NCT01586455); NCT00003336 (cord blood alone); NCT01003912 (an *in utero* protocol), or HuCNS-SC (NCT00337636). As opposed to disorders that feature brain injury without an underlying genetic defect (such as cerebral palsy related to prematurity), genetic disorders likely cannot be effectively treated with autologous transplants, necessitating the use of a conditioning regimen followed by immunosuppression to avoid rejection of infused allogeneic hematopoietic donor cells, and to prevent the development of graft-versus-host disease (GVHD). These measures put the patient at risk for life-threatening opportunistic infections. The optimal conditioning and immunosuppressive regimens appropriate to each form of delivered stem cell therapy largely remain to be determined. However, in general, children tolerate more intensive chemotherapy protocols than adults, and patients with higher pre-transplant disability have higher morbidity and mortality related to transplant. Despite these differences, and the inherent risks that come with the use of cell-based therapies, responsible centers are providing potential treatment options for fatal diseases that otherwise would not exist while collecting critical prospective data regarding the safety and efficacy of both peripheral (umbilical and bone marrow) stem cell transplant and HuCNS-SC therapies.

Studies of cross-correction, as occurs in CLN2, have shown that a diffusible enzyme can be provided by the producing cell, be taken up via mannose 6-phosphate receptors, and can be appropriately delivered to the lysosomal system, restoring function *in vitro* [7]. Studies in CLN1-deficient mice have shown a benefit of cortical implantation of HuCNS-SC, demonstrating engraftment, diminished neuropathology, enhanced neuronal preservation, and amelioration of symptoms [8]. Combining stem cell therapy with other treatment, such as adeno-associated virus gene therapy, has yielded promising results in preclinical trials in the CLN1 mouse [9]. Given the possibility of cross-correction, it would appear that diseases arising from defects in soluble enzymes such as CLN1 and CLN2 would be better candidates for a stem cell therapy as compared to disorders associated with an integral membrane protein such as CLN3.

But not so fast. X-linked cererbral adrenoleukodystrophy (XL-cALD) is caused by a defect in a transmembrane peroxisomal protein, and therefore is not amenable to cross-correction, as would be expected with a soluble enzyme deficiency. Yet bone marrow stem cell transplant at the first sign of progressive CNS disease is the gold standard therapy for cerebral XL-cALD, ameliorating further disability and slowing disease progression in

transplanted patients [10]. Exciting results also suggest that *ex vivo* gene therapy, restoring the missing gene product in hematopoietic precursors, could arrest disease progression in advanced stage XL-cALD patients [11]. If this is not due to cross-correction, what drives these findings?

Perhaps other mechanisms are at work. Aberrant or mislocalized protein or lipid may lead to storage [12] or excretion [13] from the cell in non-traditional ways, perhaps as a means to try to protect the cell from toxic accumulation. Such material could potentially be broken down by healthy engrafted stem cells. It is possible that the implantation of robust cells capable of limiting this spread could ameliorate pathology. However, it is also possible that healthy donor SCs could be hijacked by toxic aggregates as has been shown to occur with α-synuclein in Parkinson Disease [14].

In addition, whether substrate accumulation or anaplerotic depletion of metabolic precursors necessary for the synthesis of downstream molecules drives disease is still debated in many forms of LSDs, including the NCLs. Cell-based therapies may provide a means of replenishing needed metabolic intermediates.

Neuroimmune mechanisms also contribute to pathology. Although attention appropriately focuses on central nervous system manifestations, other organ system exhibit pathology in NCL. CLN3 $^{-/-}$ mice show signs of altered T cell subsets [15] and evidence of impaired blood-brain barrier integrity [16,17]. Within the brain, reactive astrocytosis and microglial activation are demonstrable in affected brain regions [18]. Could repopulating diseased bone marrow with healthy clones diminish abnormal immune activation and ultimately result in neuroprotection? The jury is still out.

Pathogenic autoantibodies (targeting glutamic acid decarboxylase (GAD65) and α-fetoprotein) have been identified in both patients and mice deficient in CLN3 [19]. Remarkably, mouse models treated with mycophenolate have shown increased survival and diminished disability [20], providing proof-of-principle evidence that an inherited storage disorder can potentially be treated with immunosuppressive agents. A phase I clinical trial evaluating the safety and efficacy of immunosuppression in CLN3 is now underway (NCT01399047). It is conceivable that in some cases, it may not be the primary intervention (stem cell transplant) alone that might prove efficacious, but the supportive therapy used to deliver this treatment (immunosuppression) could have positive effects. If realized, this would not be the first time that a “vehicle” (i.e. valproate, cyclodextrin) exerts therapeutic effects on its own.

Stem cell therapies remain highly experimental treatment prospects for the NCLs. However, they hold promise, although that promise may come with substantial risk depending on the treatment paradigm being employed. Additional trials are clearly needed to establish when and if stem cell therapies should be applied to NCL, and if so, which forms of the disease are most likely to benefit from such therapies. However, past experience would suggest that in order to ameliorate disease, stem cell delivery should occur as early in the disease process as possible, before irreversible loss of axons, neurons, and glia occur.

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