Addi and Cassi hydroxy-propyl-beta-cyclodextrin compassionate use clinical study

Treatment Plan Version # 2

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Study Site: Renown Hospital, Reno NV

Patients: Addi and Cassi Hempel

Niemann Pick Type C disease (NPC) is an autosomal recessive lysosomal storage disease characterized by progressive neurodegeneration. More than 250 mutations of the NPC1 gene located on chromosome 18 have been identified. Although NPC has a highly variable phenotype, the classic presentation occurs in middle to late childhood with insidious onset of ataxia, vertical supranuclear gaze palsy, and dementia. Other features include dystonia, dysarthria and dysphagia eventually becoming disabling. Death typically occurs in the late second or third decade from aspiration pneumonia. Definitive diagnosis of NPC is based upon impaired cholesterol esterification and positive filipin staining in cultured fibroblasts.

For expert review of NPC please see:
http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=npc and
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=257220 .

Addi and Cassi Hempel (DOB 1/23/2004), identical twin Caucasian females, received a definitive diagnosis of NPC in October, 2007. The girls have been receiving miglustat (Zavesca®) 100 mg BID for almost one year. In addition, the children are receiving nutritional supplements including curcumin.

Both children have been participating in a study at the National Institutes of Health designed to track the progression of NPC disease. The children were last examined at the NIH in July of 2008. Both children continue to exhibit hepatosplenomegaly and clinical deterioration consistent with disease progression as manifested by severe neurological symptoms including cerebellar ataxia, dysarthria, dysphagia, vertical supranuclear palsy and cataplexy as well as progressive dementia.

The proposed treatment plan is as follows:

	Baseline (-10 – 14 days)	**Week 1**	**Weeks 2-5**	**Weeks 6-10**	**Weeks 11-15**	**Subsequent Weeks**
Dose		80 mg/kg/d; 24 hrs x 4	160 mg/kg/d; 8 hrs x 1/wk	320 mg/kg/d; 8 hrs x 1/wk	400 mg/kg/d; 8 hrs x 1/wk	TBD pending protocol amendment
Mediport	X					
Physical exam	X	X	X	X	X	
Neruological exam	X	X	X	X	X	
Volumetric CT	X					X
Renal Function (GFR)	X					X
Vital sign	X	Q 15 min x 4 + Q 30 min x 2 + Q 240 min x 5	Q 15 min x 4 + Q 30 min x 2 + Q 240 min	Q 15 min x 4 + Q 30 min x 2 + Q 240 min	Q 15 min x 4 + Q 30 min x 2 + Q 240 min	
Renal labs[1]	X	X	X	X	X	
Hematology[2]	X	X	X	X	X	
Chemistry[3]	X	X	X	X	X	
Biomarker sample (15 ml whole blood)	X	X	X	X	X	
Urinary cholesterol sample 10 ml	X	X	X	X	X	

[1] Serum BUN/Cr; am spot urine Pr/Cr; UA
[2]CBC with Platelets
[3]Amylases, AST, ALT, bilirubin

- **Catheterization.** A MediPort™ central venous catheter will be surgically implanted into the subclavian vein 10 days to 2 weeks prior to initial HPBCD infusion.
- **Baseline Clinical Assessment.** Prior to the initiation of HPBCD infusion both children will have the following assessments performed:
    - Complete physical and neurological exam which will be videotaped
    - Complete blood chemistry
    - Renal function test
    - Urinalysis
    - Volumetric CT of liver and spleen
    - A 15 ml blood sample and 10 ml urine sample will be retained for experimental purposes related to biomarkers and urinary cholesterol determinations.

- **Initial infusion.** Both children will receive a four day continuous infusion of HPBCD in the pediatric ward at Renown Medical center hospital in Reno, NV a facility equipped with a pediatric ICU. Dosage will be **80 mg/kg/day** at a rate of 20 ml/hr. The solution will be administered as prepared in sterile water for injection. The final concentration will be precise based upon the weight of the patients.

  The solutions will be prepared by a pharmacy certified by the Nevada Board of Pharmacy to prepare Compounded Sterile Products in accordance with current USP chapter 797 guidelines for aseptic processing. Specifically, for a high-risk non-sterile material received in bulk the following procedure will be employed:
    - In a ISO class 5 or cleaner room the HPBCD will be weighed and dissolved in 500 ml of sterile water using sterile containers.
    - Terminal sterilization of high-risk level CSPs by filtration shall be performed with a sterile 0.22-µm porosity filter entirely within an ISO Class 5 or superior air quality environment.
    - The sterilized solution will be placed into commercial infusion bags, under ISO class 5 or cleaner conditions, and labeled according to the pharmacy SOP with before use dating of 24 hrs in accordance with USP 797*: "For a sterilized high-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature."*

- The solutions will be delivered to the clinic no more than 4 hours prior to use.

- **Safety Monitoring.** Vital signs will be monitored every 15 minutes for the first hour during initiation of IV infusion, every 30 minutes during the second hour, and then every four hours. At the conclusion of the HPBCD infusion, and prior to any subsequent infusions, the patients will receive complete blood chemistry and urinalysis. In the unlikely event that a severe allergic reaction should occur, the following specific plan to deal with the possibility of anaphylactic or hyper-allergic response will be in place:

  A standard cardex for each patient in the clinic is prepared. This card (bright orange and on top of the clinic chart at each visit) has the name, age and weight of the child. The standard drugs for resuscitation in the event of allergy or anaphylaxis are on the chart and the doses are pre-calculated. We then arrange to have these drugs available in the clinic or hospital room, at the bedside, and draw them if needed prior to administration. The protocol for initial management includes:

  - Discontinue the drug.
  - Establish airway if necessary. Assess breathing; Supply with 100% oxygen with respiratory support as needed. Assess circulation and establish IV access. Place patient on a cardiac monitor.
  - Albuterol nebulized, 0.05 to 0.15 mg/kg in 3 ml NS every 15 minutes as necessary.
  - Diphenhydramine 1mg/kg IV or IM
  - Methylprednisolone 2 mg/kg IV

  - If patient is hypotensive:
  - Place in Trendelenburg position, head at 30-degree angle below feet.
  - IV fluid bolus, NS or LR 20 ml/kg IV over 5 to 15 minutes. Repeat as necessary.
  - Epinephrine 1:10,000, 0.01 mg/kg (0.1 cc/kg) SC or IV.

  In the event any symptoms of allergy or anaphylaxis occur, the patient will be admitted to the PICU for observation and further management.

- **Subsequent infusions.** Following the initial HPBCD infusion without adverse events, the patients will receive weekly 8 hour infusions of HPBCD for three months. Additional infusions will require a protocol amendment

and review by the FDA. The patients will initially receive **160 mg/kg/day**. If well tolerated the patients will receive additional weekly infusions. The patients will have vital signs (e.g., heart rate, blood pressure, temperature) monitored as above during the infusions, and will undergo a physical examination, including neurological assessment, and clinical laboratory measurement weekly.

- **Dosage adjustment.** In the absence of side effects or adverse events (defined as serum creatinine greater than or equal to 2.5 times baseline values or liver transaminases (AST and ALT) greater than 3 time baseline), *and upon review by the FDA of laboratory values, and at the discretion of the investigator*, **a second** dosage increases to **320 mg/kg/day** will be made. Downward adjustments in dosage may be made on a **weekly** basis at the discretion of the investigator. Similarly, **a third** monthly increase to **400 mg/kg/day** will be subject to FDA review and the discretion of the investigator. If laboratory values should be elevated above the limits, the drug will be discontinued until they return to acceptable levels. The drug may then be re-started at a dose of 10 mg/kg/day less than the most recent dose.
- **Study termination.** In the event clinically significant adverse events are observed, the study may be terminated at any time at the discretion of the investigator. Throughout the study stopping criteria will be the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v3) Grade 4 toxicity. At the end of three months treatment the data will be reviewed with the FDA and a decision whether to continue treatment will be made.
- **Therapeutic endpoints.** The primary endpoint of this study will be improvement in neurological functioning. Secondarily, arrest of disease progression will be assessed based upon independent expert review of the case report and video assessments. At three month intervals and/or at the conclusion of the study a complete physical and videotaped neurological exam will be performed. Changes in neurological status will be assessed using independent ratings of the videotapes examined by a pediatric neurologist. A volumetric CT of the liver and spleen will obtained for possible changes in hepatosplenomegaly. Following each infusion a 15 ml blood sample and 10 ml urine sample will be retained for experimental purposes related to biomarkers and urinary cholesterol determinations. Weekly assessment by the parents will examine quality of life measures and a global impression of change will be made.