BLOOD AND MARROW
TRANSPLANT
CLINICAL TRIALS NETWORK

**BMT CTN 1204**
**Reduced-Intensity Conditioning for Children and Adults with Hemophagocytic Syndromes or Selected Primary Immune Deficiencies (RICHI)**

**Modifications to Version 3.0 of the Protocol**

**The significant changes in the protocol and consent form are summarized below:**

- The sample size was expanded from 35 patients with HLH and other hemophagocytic syndromes or immune disorders to 35 HLH patients.
- Language was added to the protocol and consent regarding the risk of RPLS/PRES**.**
- Language was added to require that all occurrences of RPLS/PRES be reported via the expedited AE reporting system.
- A new appendix was added with tables of blood pressure levels according to age and weight percentiles for assistance with monitoring and control of blood pressure.

Detailed changes are listed below. Deletions to the protocol are indicated in strike-out text; additions are noted in underlined text.

***Protocol Synopsis, §Accrual Objective***
The trial will accrue a minimum of 35 HLH patients.

***§2.7.6. Blood Pressure Monitoring and Control (NEW)***
Blood pressure should be strictly controlled to prevent CNS toxicity. Patients with HLH often have experienced renal toxicity prior to HSCT. This in combination with high doses of steroids and Calcineurin inhibitors used both before and after HSCT puts these patients at risk for posterior reversible encephalopathy syndrome (PRES). Blood pressure should be monitored closely and elevations in systolic and/or diastolic pressure(s) should be treated promptly to maintain blood pressure within 10% above the baseline age-related median systolic and diastolic pressure (see Appendix G).

PRES is characterized by headache, seizures, and visual loss, as well as an abrupt increase in blood pressure. If PRES is suspected or diagnosed, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors. A negative MRI is required to exclude PRES.

***§4.2.2. Adverse Event Reporting***
Unexpected, grade 3-5 adverse events (AE) and all deaths will be reported through an expedited AE reporting system via AdvantageEDCSM. Additionally, any occurrence of posterior reversible encephalopathy syndrome (PRES) or reversible posterior leukoencephalopathy syndrome (RPLS) requires reporting through the AE reporting system. Unexpected, grade 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Expected AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 at regular intervals as defined on the Form Submission Schedule.

***§5.1 Study Design***
The study is a Phase II, non-randomized, multi-center trial. It is designed to assess overall survival 365 days after patients undergo reduced-intensity conditioning (RIC) HCT with fludarabine, melphalan, and intermediate timing of alemtuzumab for HLH or related conditions. The sample size is a minimum of 35 HLH patients.

***§5.6 Sample Size and Power Considerations***
Sample size calculations were based on an original sample size of 35 patients. After rapid accrual, the protocol was amended to include a minimum of 35 HLH patients to improve the precision of both the overall estimate and the secondary disease specific subgroup analysis.

~~The sample size is 35 patients.~~ Table 5.6.1 provides 90% confidence intervals for a variety of observed proportions. …

**Appendix B – Informed Consent and Assent**

***§1. Introduction***
This study will take about 3 years total and will include 35 HLH patients in addition to patients with other hemophagocytic syndromes or immune disorders from around the United States and Canada.

***§6. Risks and Discomforts***

- ***Risk Table for Cyclosporine***:

| Likely | Less Likely | Rare, but Serious |
|---|---|---|
| ▪ Tremors<br>▪ High blood pressure<br>▪ Kidney problems<br>▪ Headaches<br>▪ Nausea<br>▪ Vomiting<br>▪ Stomach pain or indigestion<br>▪ Swelling of the hands or feet<br>▪ Increased hair growth<br>▪ Electrolyte imbalances | ▪ Confusion<br>▪ High levels of triglycerides in the blood<br>▪ Diarrhea<br>▪ Gum enlargement<br>▪ Liver dysfunction<br>▪ RPLS/PRES[1] | ▪ Muscle cramps<br>▪ Numbness and tingling of the hands or feet<br>▪ Seizures<br>▪ Dizziness<br>▪ Red blood cell destruction<br>▪ Temporary blindness |

[1] Reversible posterior leukoencephalopathy syndrome (RPLS) also known as posterior reversible encephalopathy syndrome (PRES) – See text below for description

- ***Risk Table for Tacrolimus***

| Likely | Less Likely | Rare, but Serious |
|---|---|---|
| ▪ High blood pressure<br>▪ High blood sugar<br>▪ Anemia (low red blood cell count)<br>▪ High or low potassium levels<br>▪ Low magnesium and calcium levels<br>▪ Loss of appetite<br>▪ Diarrhea<br>▪ Nausea<br>▪ Fever<br>▪ Headache | ▪ Hair loss<br>▪ Vomiting<br>▪ Tingling sensation in the extremities<br>▪ Itching<br>▪ Rash<br>▪ Abdominal pain<br>▪ RPLS/PRES[1] | ▪ Confusion<br>▪ Painful joints<br>▪ Increased sensitivity to light<br>▪ Change in vision<br>▪ Insomnia (trouble sleeping)<br>▪ Infection<br>▪ Jaundice (skin yellowing)<br>▪ Kidney injury<br>▪ Seizures |

[1] Reversible posterior leukoencephalopathy syndrome (RPLS) also known as posterior reversible encephalopathy syndrome (PRES) – See text below for description

- ***Risk Table for Methylprednisolone and Prednisone***

| Likely | Less Likely | Rare, but Serious |
|---|---|---|
| ▪ Water retention (storing of extra water)<br>▪ Overeating<br>▪ Weaker immune system<br>▪ Temporary personality changes<br>▪ Abnormal hormone production<br>▪ High blood sugar<br>▪ Slowed growth<br>▪ Decreased bone density<br>▪ Fat accumulation causing a change in facial appearance | ▪ Headaches<br>▪ Poor wound healing<br>▪ Stomach swelling or pain<br>▪ Tissue swelling<br>▪ High blood pressure<br>▪ Stomach ulcer<br>▪ Muscle weakness<br>▪ Cataracts<br>▪ Bone cell death<br>▪ RPLS/PRES[1] | ▪ Difficulty falling asleep<br>▪ Worsening of diabetes<br>▪ Inflammation of pancreas<br>▪ Personality disturbances<br>▪ Bleeding in the stomach and intestines<br>▪ Increased pressure within the eye<br>▪ Disturbance of bone calcium (might lead to possible broken bones or permanent bone damage) |

[1] Reversible posterior leukoencephalopathy syndrome (RPLS) also known as posterior reversible encephalopathy syndrome (PRES) – See text below for description

***Potential Risk of RPLS/PRES*** (NEW – located below Risk Table for Filgrastim))

The Data Safety and Monitoring Board (DSMB) of the Blood and Marrow Transplant Clinical Trials Network is a group of transplant, HLH and immune deficiency disease and other experts that ensure the safety of patients treated on this and other trials. This group carefully monitors the experience of patients to make sure that the side effects that they experience are not unusual or more frequent or more severe than would be expected.

The DSMB has noted that patients transplanted on the clinical trial BMT CTN 1204 have a higher than expected occurrence of a usually uncommon (<5%) complication called reversible posterior leukoencephalopathy syndrome (RPLS) also known as posterior reversible encephalopathy syndrome

(PRES). Patients with RPLS/PRES have confusion and other changes in their ability to think. Sometimes, they experience seizures, sleepiness or, rarely, loss of consciousness. RPLS is diagnosed with an MRI of the brain. In transplant patients, it is usually caused by some of the drugs used to prevent or treat graft versus host disease. It can often, but not always, be prevented by very careful control of blood pressure. It is treated by changing graft versus host disease drugs, controlling blood pressure and/or giving anti-seizure medicines. Three out of thirty-five patients on BMT CTN 1204 have developed RPLS/PRES; all were successfully treated for this complication. Thus far, no RPLS/PRES has been observed in any patient more than 6 months from their date of transplant. We believe that children who are on prednisone or other corticosteroids, or immunosuppressive drugs such as cyclosporine or tacrolimus or have high blood pressure are more likely to develop RPLS/PRES.

If you/your child experience any of these side effects or changes in mental status, you should contact your/your child's transplant physician right away, since early treatment is important. It is also important that any blood pressure medication be taken as prescribed to decrease the risk of RPLS/PRES.

***Appendix G, Blood Pressure Levels for Boys by Age and Height Percentile*** (NEW) (http://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf).

***Appendix ~~G~~ H, References***