Immunotherapy Trial for Kids with Relapsed or Refractory Leukemias and Solid Tumors

American Family Children’s Hospital, part of the University of Wisconsin Carbone Cancer Center, announces a phase I clinical immunotherapy trial for children and adolescents with relapsed/refractory leukemias and solid tumors. The trial combines a graft-engineered haploidentical stem cell transplant with post-transplant immunotherapy to boost graft-versus-tumor effects and eradicate residual cancer cells.

Allogeneic hematopoietic stem cell transplantation (HSCT) is curative for many patients with hematologic malignancies. The anti-leukemia effects of allo-HSCT result from 1) chemotherapy and/or radiation used for the conditioning regimen and, 2) the graft-versus-leukemia effect resulting from transplantation of the donor immune system.

Haploidentical HSCT, (i.e. transplantation from a donor identical for only one haplotype - in most cases a parent or sibling) has the benefit of guaranteeing donor availability for nearly every patient and avoiding the delay involved in searching for a matched, unrelated donor with the potential consequence of disease progression in the interim[1]. To avert graft-versus-host disease (GVHD), the two most common haplo-HSCT approaches (CD34+ selection and administration of post-transplant cyclophosphamide) profoundly deplete T cells. In addition, both methodologies remove immune populations critical for a graft-versus-tumor (GVT) effect, namely natural killer (NK) cells and TCR γδ T cells [2, 3]. After transplantation, immune reconstitution of these elements requires several months. This prolonged period of profound immune deficiency increases the risk of infection and blunts the GVT effect at a crucial time when minimal residual disease could potentially be eradicated, and the patient cured.

The graft engineering method employed in the UW – AFCH trial selectively depletes TCR αβ T cells and B cells (via immunomagnetic technique) from a G-CSF-mobilized donor graft prior to HSCT, ensuring that large amounts of NK cells, TCR γδ T cells and other immune cells are transplanted together with non-manipulated hematopoietic stem cells. This form of graft engineering, co-developed by the Principal Investigator of this study, Mario Otto, MD, PhD, has shown profound depletion of undesirable TCR αβ T cells from the graft, associated with very low rates of GVHD, and fast engraftment in national and international studies [4-6]. Preference is given to a donor with favorable KIR/KIR-Ligand mismatch to boost NK alloreactivity[7]. The myeloablative conditioning regimen for patients with leukemia consists of rATG, fludarabine, thiotepa and TBI. Patients with solid tumors receive a reduced-intensity conditioning regimen with rATG, fludarabine, thiotepa and melphalan. To activate TCR γδ T cells and NK cells post-transplant, all patients receive the aminobisphosphonate zoledronate starting at post-transplant day +28, administered every 4 weeks for a total of 5 doses [8].

The primary study endpoints of this phase I safety and feasibility trial are engraftment and incidence and severity of grade II-IV acute GVHD experienced within 100 days post-transplant. Secondary and exploratory endpoints are immune reconstitution, activity of immune cell subsets and disease-free survival at Day 100, 1 year and 2 years post-transplant.

Key eligibility criteria are:

**General:**
1. At least 1 biologic parent or close family member (≥ 18 years of age) who can serve as (haploidentical) stem cell donor
2. Must meet standard organ function requirements for HSCT
3. Life expectancy ≥ 3 months and Karnofsky/Lansky score ≥ 60
4. Must have fully recovered from acute toxic effects of all previous therapies, and study enrollment no earlier than 3 months after preceding HSCT

Hematologic Malignancy:
No HLA identical sibling or suitable unrelated donor, or time needed to find an acceptable unrelated donor match would likely result in disease progression such that the patient may become ineligible for any type of potentially curative transplant
1. Very high risk or relapsed ALL or AML in current remission
2. Myelodysplastic syndrome
3. Relapsed Hodgkin lymphoma or NHL who failed autologous transplant or autologous transplant not deemed appropriate

Solid Tumors:
1. Relapsed neuroblastoma, Wilms tumor, Ewing sarcoma, rhabdomyosarcoma, osteogenic sarcoma, or other solid tumor who failed autologous transplant or autologous transplant not deemed appropriate
2. 1st CR, but very-high risk features (i.e., <20% survival with conventional therapy)

This trial is open and recruiting patients.

Two other unique clinical trials offered at UW Health American Family Children’s Hospital are:
1. **Phase I Trial of Ex-Vivo Expanded Haploidentical NK Cells and Hu14.18-IL2 for Children with Relapsed/Refractory Neuroblastoma (Clinicaltrials.gov ID: NCT03209869)**
   This study is evaluating the feasibility of infusing multiple cycles of ex-vivo activated and expanded allogeneic NK cells (AE NK cells), given with hu14.18-IL2, an anti-GD2 immunocytokine, to treat children with relapsed or refractory neuroblastoma. Patients will receive lymphodepletive chemotherapy prior to infusion of the AE NK cells. The hu14.18-IL2 will then be administered once daily for 7 days. Cycles may be repeated every 4 – 6 weeks.
   Key Eligibility:
   - Ages 6 months – 21 years
   - Relapsed or refractory neuroblastoma
   - Active disease as assessed by CT/MRI, MIBG scan or bone marrow histology
   - Available haploidentical NK cell donor

2. **CLOVER-2: A phase I trial of CLR 131, a targeted radiotherapy, to treat children and adolescent solid cancers, lymphomas and malignant brain tumors (ClinicalTrials.gov ID: NCT03478462)**
   CLR 131 is a systemically administered, tumor-targeted radiopharmaceutical which takes advantage of a specific feature of cancer cell membranes. The drug enters cancer cells via lipid rafts that are highly expressed in practically all cancer cells, in contrast to normal cells. The drug is retained in tumors as it is quickly integrated in the membrane of cancer cells and their cellular organelles where it delivers its anti-cancer radioactive properties. This is a phase I, dose escalation study for pediatric patients with relapsed or refractory solid tumors and brain tumors that have failed standard treatments.
Key eligibility:
- ages ≥ 2 years and ≤ 21 years
- performance status ≥ 60
- ability to collect an autologous stem cell backup
- measurable disease (≥ 15 mm for extracranial tumors, ≥ 10 mm for CNS tumors)
- patients who have undergone previous autologous stem cell transplant must be at least 3 months from transplant

References