Investigator: Gopin Saini (1)
Investigator: Alice Bertaina (1)
Investigator: Paul Grimm (2)
  (1) Pediatrics—Stem Cell Transplantation
  (2) Pediatrics—Nephrology

Title: HSCT before RT for Patients with Genetic Disorders

Summary:
The Data Studio Workshop brings together a biomedical investigator with a group of experts for an in-depth session to solicit advice about statistical and study design issues that arise while planning or conducting a research project. This week, the investigator(s) will discuss the following project with the group.

Renal transplantation (RT) is the treatment of choice for eligible patients with end-stage renal disease. Short- and intermediate-term outcomes of renal allografts have improved due to fewer early rejections and to better standardized immunosuppressive treatment strategies. The induction of immune tolerance for the renal allograft is the ultimate goal in the field of RT to enhance long-term outcomes significantly. This is crucial for pediatric patients with genetic disorders because they need multiple RTs during their lifetime in the absence of immune tolerance.

We are planning a single-center, non-randomized, non-controlled, open-label Phase 1 trial. The study population will consist of pediatric-young adult patients requiring either a first or subsequent RT due to underlying genetic or immunologic disease. We will test a treatment modality consisting of alpha-beta-positive T-cell/CD19 B-cell depleted hematopoietic stem cell transplantation (HSCT) followed by RT from a mismatched related or unrelated donor. In this trial, dose-finding will not be needed because both the HSCT and RT are standard-of-care interventions, albeit for different indications. Our aim for each patient is to achieve full donor chimerism, perform RT with minimal immunosuppression (IS), and taper the IS quickly to withdrawal.

Based on the trial objectives, we have two primary endpoints: withdrawal of IS by Day +90 following RT; normal renal function in the absence of IS at 1 year. We will pause the trial if any of the following occur: a death related to HSCT; primary HSCT graft failure (we can tolerate up to 20% whereas the current rate is less than 10%); Grade III–IV acute GvHD (we can tolerate up to 20% whereas the current rate is less than 10%).

Questions:
Our statistical questions cover three areas: trial design, sample size, and safety stopping rules.

1. Trial Design
   (a) Which design (e.g., basket trial, seamless Phase 1/2) should we consider for this clinical trial?
   (b) Can the design accommodate both a safety run-in cohort and an expansion cohort for evaluation of safety and efficacy?
   (c) Do the primary endpoints capture the objective of study? If not, are there any alternatives?

2. Sample Size
   (a) How do we calculate sample size?
   (b) Should we base it on safety of the investigational intervention, HSCT?
   (c) Should we base it on efficacy over standard practice?

3. Safety Stopping Rules
(a) How do we develop safety stopping rules?
(b) Should we base it on death related to HSCT?
(c) Should we base it on primary HSCT graft failure?
(d) Should we base it on excessive Grade III-IV acute GvHD?

Zoom Meeting Information

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