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A Phase II Study of Myeloablative and Reduced-Intensity Conditioning Regimens for Children and Young Adults with Acute Myeloid Leukemia or Myelodysplastic Syndrome Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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Protocol Synopsis

Protocol Title	A Phase II Study of Myeloablative and Reduced-Intensity Conditioning Regimens for Children and Young Adults with Acute Myeloid Leukemia or Myelodysplastic Syndrome Undergoing Allogeneic Hematopoietic Stem Cell Transplantation
Version/Date	Version 5.0: September 03, 2020
Clinical Phase	Phase II
Trial Site	University of Pittsburgh Medical Center (UPMC) • UPMC Children's Hospital of Pittsburgh (CHP)
Primary Investigator	Randy Windreich, MD
Primary Objective	To determine the safety and preliminary efficacy of achieving acceptable rates of event-free survival at 6 months in pediatric patients receiving a myeloablative preparative regimen including Busulfan, Fludarabine and Thiotepa or a reduced-intensity preparative regimen including Alemtuzumab, Hydroxyurea, Fludarabine, Melphalan and Thiotepa prior to hematopoietic stem cell transplantation for high-risk acute myeloid leukemia and myelodysplastic syndrome.
Secondary Objective	• To describe the pace of neutrophil and platelet recovery. • To describe the incidence of acute GVHD (II-IV, III-IV) and chronic GVHD. • To determine the treatment-related mortality (TRM), overall survival (OS), and disease-free survival (DFS) by Days 100 and 180 post-transplant. • To evaluate the pace of immune reconstitution. • To measure Day 0 alemtuzumab levels, if available, and correlate with rate of relapse, rate of viral infections, and pace of immune reconstitution. • To compare outcomes with historically-used “standard” conditioning regimen of busulfan and cyclophosphamide in terms of above objectives as well as short- and long-term complications.
Hypothesis	We hypothesize that a myeloablative fludarabine/busulfan/thiotepa (FLU/BU/THIO) regimen, along with the addition of alemtuzumab for CD52-positive malignancies and mismatched grafts, provides improved overall survival and event-free survival rates in pediatric patients undergoing myeloablative transplants; the reduced-intensity regimen will be well-tolerated and allow pediatric patients with significant comorbidities that would otherwise preclude them from transplantation to receive a potentially life-saving allogeneic stem cell transplant; and, similar to its action on normal HSCs, pre-transplant G-CSF may disrupt the interaction of leukemic stem cells with the marrow microenvironment, thereby sensitizing these cells to genotoxic stresses.
Study Design	This is a single-center, prospective, non-randomized, dual-arm, phase II study evaluating the safety and efficacy of achieving acceptable rates of event-free survival in pediatric patients receiving either a myeloablative conditioning (MAC) regimen including Busulfan, Fludarabine and Thiotepa or a reduced-intensity conditioning (RIC) regimen including Alemtuzumab, Hydroxyurea, Fludarabine, Melphalan and Thiotepa prior to blood and marrow transplantation for high-risk acute myeloid leukemia or myelodysplastic syndrome.

Planned Sample Size	Expected accrual to this study is 3-4 patients per year based on the last 5 years' average. We anticipate enrollment of 16 patients receiving stem cell transplant. Total accrual time could be as long as 4 years, or more, if the study is not stopped early.
Duration of Treatment	Subjects will be followed for one year post stem cell transplant, and data may be obtained from the subjects' medical charts for an additional three years, post stem cell transplant.
Inclusion Criteria: Study Entry	Individuals must meet all the following criteria to be eligible for this study. • Subject, parent, or legal guardian, if applicable, must have given written informed consent. For patients ≤ 17 years of age who are developmentally able, assent or affirmation will be obtained. • Age 0-26, inclusive, at time of consent. • Diagnosis of myelodysplastic syndrome or acute myeloid leukemia, either high-risk (defined below), relapsed or primary refractory, MRD-positive without circulating myeloblasts or active extramedullary disease at the time of transplant. Active marrow disease is permitted. High-risk AML features are defined by the following: RAM phenotype; adverse cytogenetic abnormalities of monosomy 5, monosomy 7, 5q deletion, or other unfavorable prognostic markers according to cytogenetics, FISH, or next generation sequencing (NGS); presence of FLT3 positive internal tandem duplication (FLT3/ITD+), particularly high allelic ratio; treatment-related AML; or positive minimal residual disease (MRD) at end of Induction I. • Stem cell sources include bone marrow, peripheral blood stem cells, or umbilical cord blood. Related bone marrow, peripheral blood stem cell, or cord blood unit: sibling should be HLA-matched at A, B, and DR-B1 loci. Unrelated cord blood unit should be at a minimum of 4/6 matched at antigen level on HLA A and B, and allele level at HLA DR-B1 loci. Unrelated bone marrow or peripheral blood stem cell donor should be HLA allele level matched at DR-B1. • Minimum pre-freezing cell dose for cord blood units: 3 x 10^7 total nucleated cells/kg and 1.5 x 10^5 CD34+ cells/kg. If this is not attainable, then double cord blood transplant should be considered. • Subject must have adequate performance status: Lansky score ≥60% for patients <16 years, Karnofsky score ≥60% for patients ≥16 years. • Subject must have adequate pre-transplant organ function to **undergo one of the two conditioning regimens, either the myeloablative conditioning (MAC) OR reduced-intensity conditioning (RIC) regimen.** If a subject does not meet the following organ function criteria for the MAC regimen, the RIC regimen will be considered if eligibility criteria is met. The RIC regimen may also be considered, regardless of MAC eligibility, if deemed appropriate by the Principal Investigator and/or treating physician. **Pre-transplant organ function criteria for Myeloablative Conditioning regimen:** ○ Renal: creatinine clearance or radioisotope GFR ≥70 mL/min/1.73 m2. ○ Hepatic: total bilirubin ≤2.0 mg/dL unless the increase in bilirubin is attributable to Gilbert's syndrome; and SGOT (AST), SGPT (ALT), and Alkaline Phosphatase <4 x upper limit of normal (ULN) for age. ○ Cardiac: normal cardiac function by echocardiogram or radionuclide scan, as defined by left ventricular ejection fraction at rest >45% or shortening fraction >26%. ○ Pulmonary: FEV1, FVC, and DLCO (corrected for hemoglobin) ≥50% of predicted; if unable to perform pulmonary function tests, then oxygen saturation ≥92% on room air. **OR** **Pre-transplant organ function criteria for Reduced-Intensity Conditioning regimen:** ○ Renal: creatinine clearance or radioisotope GFR ≥70 mL/min/1.73 m2.

	○ Hepatic: total bilirubin ≤2.5 mg/dL unless the increase in bilirubin is attributable to Gilbert's syndrome; and SGOT (AST), SGPT (ALT), and Alkaline Phosphatase <5 x upper limit of normal (ULN) for age. ○ Cardiac: normal cardiac function by echocardiogram or radionuclide scan, as defined by left ventricular ejection fraction at rest >40% or shortening fraction >26%. ○ Pulmonary: FEV1, FVC, and DLCO (corrected for hemoglobin) ≥40% of predicted; if unable to perform pulmonary function tests, then oxygen saturation ≥92% on room air. • HIV and HTLV negative, by either PCR or serology. • Negative pregnancy test for females ≥10 years old or who have reached menarche. • All females of childbearing potential and sexually active males must agree to use an FDA approved method of birth control for up to 12 months after HSCT or for as long as they are taking any medication that may harm a pregnancy, an unborn child or may cause a birth defect.
Exclusion Criteria: Study Entry	Individuals who meet any of the following criteria are not eligible for this protocol. • Uncontrolled bacterial, viral, fungal, or other infection at the time of cytoreduction, defined by positive blood cultures and/or fevers >38.0 within 24 hours of start of conditioning therapy. • Females who are pregnant or who are lactating. • Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study. **Additional Exclusion Criteria for Myeloablative Conditioning (MAC) Only** Individuals who meet any of the following criteria are not eligible for the MAC regimen. • Recipient of either an autologous or allogeneic stem cell transplant within 3 months of the start of conditioning. • Patients with any inherited bone marrow failure syndrome including, but not limited to, Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenital or Down syndrome (defined as either constitutional trisomy 21 or constitutional mosaicism of trisomy 21).
Efficacy Endpoint	• Absence of leukemia or dysplasia at 6 months post-HSCT and beyond. • Achievement of full donor chimerism.

- To measure Day 0 Alemtuzumab levels, if available, and correlate with rate of relapse, rate of viral infections, and pace of immune reconstitution.
- To compare the outcomes with historically-used "standard" conditioning regimen of Busulfan and Cyclophosphamide in terms of above objectives as well as short- and long-term complications.

2.4.3 Efficacy Endpoints

- Absence of leukemia or dysplasia at 6 months post-HSCT and beyond.
- Achievement of full donor chimerism.

2.5 STATISTICAL ANALYSIS

2.5.1 Sample Size Determination

Expected accrual to this study is 3-4 patients per year based on the last 5 years' average. We anticipate enrollment of 16 patients receiving stem cell transplant. Total accrual time could be as long as 4 years, or more, if the study is not stopped early.

2.5.2 Efficacy Analysis

The study sample for efficacy will be patients who receive HSCT (n=12). Efficacy will be defined by the following criteria:

- Absence of leukemia or dysplasia at 6 months post-HSCT and beyond.
- Achievement of full donor chimerism.

Efficacy will be analyzed as a case series, with rates for key efficacy criteria reported with 95% Wilson (score) confidence intervals. For example, if 4/12 patients receiving HSCT are leukemia-free by 2-year milestone post-HSCT, the rate of independence of absence of leukemia would be reported as 0.33 (95% CI 0.14-0.61).

2.5.3 Safety Analysis

All reported adverse events will be coded using the NCI common toxicity criteria. The number and percent of patients reporting adverse events will be quantified for each phase of therapy (HSCT, post-HSCT).

2.5.4 Handling Missing Data

Standard procedures will be used to ensure that data are as complete and accurate as possible. We will not impute values for subjects with missing data.

2.5.5 Data Management

Data will be generated from standard of care procedures, tests, etc. and will be available in the subjects' medical records.

3 SUBJECT POPULATION AND CLINICAL SITES

3.1 Eligibility for Study Entry

3.1.1 Inclusion Criteria