Treosulfan-Based Conditioning Regimen Before a Blood or Bone Marrow Transplant for the Treatment of Bone Marrow Failure Diseases (BMT CTN 1904)

Status: Recruiting

Eligibility Criteria

Age: 1 year to 49 years old

This study is NOT accepting healthy

Healthy Volunteers: volunteers

Inclusion Criteria:

• Patient must be >= 1.0 year of age and less than 50.0 years of age at the time of enrollment (i.e. patient must have celebrated their 1st birthday when enrolled and must NOT have celebrated their 50th birthday when enrolled; 49.99 years)

• Underlying BMFD treatable by allogenic HCT

• Shwachman-Diamond syndrome

• Criteria for Diagnosis:

• A pathogenic mutation(s) for Shwachman-Diamond syndrome

• For those patients tested but lacking a genetic mutation they must meet both **** criteria below:

• Exocrine pancreatic dysfunction as defined by at least one of the following:

• Pancreatic isoamylase below normal (age >= 3 years old), OR

• Fecal elastase < 200, AND

• Bone marrow failure as evidence by at least one of the following:

• Intermittent or persistent neutropenia (absolute neutrophil count < 1,500/uL), OR

• Hypo-productive anemia with a hemoglobin concentration below the age-related adjusted norms, OR

• Unexplained macrocytosis, OR

• Platelet count < 150,000/uL without alternative etiology, OR

• Hypocellular bone marrow

• Indications for HCT:

• Severe neutropenia (absolute neutrophil count [ANC] < 500/uL), OR

• Severe anemia (hemoglobin < 8 g/dL) or transfusion-dependent anemia, OR

• Severe thrombocytopenia (platelet count < 20,000/uL) or transfusion-dependent thrombocytopenia, OR

• Additional clinical or laboratory data may be considered for protocol eligibility following review by protocol 1904 eligibility review committee (ERC). In addition, patients with severe or recurrent infections will be reviewed by the ERC if they do not meet the indications for transplant listed above

• Diamond Blackfan Anemia

• Criteria for Diagnosis:

• A pathogenic mutation for Diamond Blackfan anemia

• For those patients tested but lacking a genetic mutation the patient must meet the first *** criteria and at least one of the subsequent *** criteria listed below:

• History of deficiency of erythroid precursors in an otherwise cellular bone marrow AND,

• Reticulocytopenia, OR

• Elevated adenosine deaminase activity, OR

• Elevated hemoglobin F, OR

• Macrocytosis, OR

• Congenital anomalies

• Indications for HCT:

• Red blood cell (RBC) transfusion dependent anemia despite an adequate trial of steroids; OR

• Additional clinical or laboratory data may be considered for protocol eligibility following review by protocol 1904 ERC

• Congenital Sideroblastic anemia

• Criteria for Diagnosis:

• A pathogenic mutation(s) for sideroblastic anemia

• For those patients tested but lacking a genetic mutation:

• Presence of ringed sideroblasts in the bone marrow excluding acquired causes of ringed sideroblasts such as lead poisoning & zinc toxicity

• Indications for HCT:

• Severe anemia (hemoglobin < 8 g/dL) or transfusion-dependent anemia OR

• Additional clinical or laboratory data may be considered for protocol eligibility following review by protocol 1904 ERC

• GATA2 mutation with associated marrow failure

• Criteria for Diagnosis: ** A pathogenic mutation(s) for GATA2

• Indications for HCT:

• Severe neutropenia (ANC < 500/uL), OR

• Severe anemia (hemoglobin < 8 g/dL) or transfusion-dependent anemia, OR

• Severe thrombocytopenia (platelet count < 20,000/uL) or transfusion-dependent thrombocytopenia, OR

• Additional clinical or laboratory data may be considered for protocol eligibility following review by protocol 1904 ERC. In addition, patients with severe or recurrent infections will be reviewed by the ERC if they do not meet indications for transplant listed above

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• SAMD9 or SAMD9L disorders

• Criteria for Diagnosis: ** A pathogenic mutation(s) for SAMD9 or SAMD9L

• Indications for HCT:

• Severe neutropenia (ANC < 500/uL), OR

• Severe anemia (hemoglobin < 8 g/dL) or transfusion-dependent anemia, OR

• Severe thrombocytopenia (platelet count < 20,000/uL) or transfusion-dependent thrombocytopenia, OR

• Additional clinical or laboratory data may be considered for protocol eligibility following review by protocol 1904 ERC

• Congenital amegakaryocytic thrombocytopenia

• Criteria for Diagnosis:

• A pathogenic mutation(s) for congenital amegakaryocytic thrombocytopenia.

• For those patients tested but lacking a genetic mutation the patient must meet criteria below:

• Thrombocytopenia early in life, AND

• History of bone marrow demonstrating megakaryocyte hypoplasia

• Indications for HCT:

• Severe thrombocytopenia (platelet count < 20,000/uL) or transfusion-dependent thrombocytopenia, OR

• Neutropenia defined as an ANC < 500/uL, OR

• Severe anemia (hemoglobin < 8 g/dL) or transfusion-dependent anemia, OR

• Additional clinical or laboratory data may be considered for protocol eligibility following review by protocol 1904 ERC

• Paroxysmal nocturnal hemoglobinuria

• Criteria for Diagnosis:

• Paroxysmal nocturnal hemoglobinuria (PNH) clone size in granulocytes >= 10%, AND

• Complement mediated intravascular hemolysis with an elevated LDH (above institutional upper limits of normal)

• Indications for HCT:

• PNH with thrombosis despite adequate medical management, OR

• PNH with intravascular hemolysis requiring transfusion support despite adequate medical management, OR

• Additional clinical or laboratory data may be considered for protocol eligibility following review by protocol 1904 ERC. In addition, patients with PNH and cytopenias may be considered for the protocol eligibility following review by protocol 1904 ERC

• An undefined BMFD: a patient with a BMFD for whom a genetic mutation responsible for their bone marrow failure phenotype has not been identified (excluding PNH) will be eligible for this clinical trial following approval by Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1904 ERC * A BMFD with a known genetic mutation but not listed above will be eligible for this clinical trial following approval by BMT CTN 1904 ERC

• Patient and/or legal guardian must sign informed consent prior to initiation of conditioning for BMT CTN 1904

• Females and males of childbearing potential must agree to practice 2 effective methods of contraception at the same time or agree to abstinence

• Note: The following patients MUST be reviewed by the BMT CTN 1904 ERC in order to determine if they are eligible for this trial:

• All patients with Shwachman-Diamond syndrome, Diamond Blackfan anemia, congenital sideroblastic anemia, and congenital amegakaryocytic thrombocytopenia who have had genetic testing and lack a genetic mutation

• All patients with an undefined BMFD: a patient with a BMFD for whom a genetic mutation responsible for their bone marrow failure phenotype has not been identified, excluding PNH

• All patients with a BMFD and a known genetic mutation that is not listed above

• All patients with GATA2 mutation and associated marrow failure

• All patients with SAMD9 or SAMD9L disorders

• There may be circumstances where a treating physician will consider a transplant for a patient with a BMFD who does not meet all the criteria listed under "indications for HCT". In these situations, treating physicians may submit their patient to the BMT CTN 1904 ERC for review in order to determine if the patient is eligible for this clinical trial based on additional clinical or laboratory information

• Many patients with BMFD can have bone marrow evaluations that raise concern for possible myelodysplastic syndrome (MDS) including but not limited to dysplastic bone marrow evaluations or cytogenetic abnormalities. However, in patients BMFD these findings are not necessarily diagnostic or consistent with MDS. Therefore, given the complexities of diagnosing MDS in patients with BMFD, all patients with bone marrow evaluations concerning for possible MDS should be submitted to the ERC for review to confirm or exclude MDS. This is particularly important as we do not want to exclude potentially eligible patients due to an incorrect diagnosis of MDS

• HLA-MATCHED RELATED DONOR: HLA-matched sibling: Must be a minimum HLA-6/6 matched to the recipient at HLA-A, -B (serologic typing) and DRB1 (high-resolution typing)

• HLA-MATCHED RELATED DONOR: HLA-matched related (phenotypic match): Fully matched for HLA-A, -B, -C, -DRB1, and DQB1 by high-resolution typing.

• HLA-MATCHED RELATED DONOR: If a genetic mutation is known for the patient, the HLA-matched related donor [either HLA-matched sibling or HLA-matched related (phenotypic match)] must be screened for the same genetic mutation if clinically appropriate and should be confirmed to not have the same genetic disease (this does not include patients with PNH). Consult the protocol team with questions

• HLA-MATCHED RELATED DONOR: If a patient has an undefined BMFD (a patient with a BMFD for whom a genetic mutation responsible for their bone marrow failure phenotype has not been identified), the HLA-matched related donor [either HLA-matched sibling or HLA-matched related (phenotypic match)] must have an evaluation as directed by the treating physician to confirm that the donor does not have the same underlying disease. This will include a complete blood count (CBC) with differential and potentially a bone marrow evaluation or other studies as directed by the treating physician

• UNRELATED DONOR: Fully matched for HLA-A, -B, -C, -DRB1, and DQB1 by high-resolution typing

• UNRELATED DONOR: Mismatched for a single HLA-class 1 allele (HLA-A, -B, or -C) by high-resolution typing; OR

• UNRELATED DONOR: Mismatched for a single HLA DQB1 allele or antigen by high-resolution typing * Note: donor patient (DP) matching per institutional practice

• DONOR SELECTION RECCOMENDATIONS: in the case where there are multiple donor options, donors should be selected based on the following priority numbered below:

• Unaffected fully HLA-matched sibling

• Unaffected fully phenotypically HLA-matched related donor

• Fully HLA-matched unrelated donor

• Unrelated donor with single allele or antigen level mismatch at DQB1

• Unrelated donor with single allele level mismatch at class 1 (HLA-A, -B, or -C)

Exclusion Criteria:

• Patients with idiopathic aplastic anemia, Fanconi anemia, dyskeratosis congenita, and congenital neutropenia

• Patients with MDS as defined by the World Health Organization (WHO) or leukemia

• Prior allogeneic HCT

• Patient's weight =< 10.0 kg (actual body weight and adjusted body weight) at time of study enrollment

• Lansky (patients < 16 years of age) or Karnofsky (patients >= 16 years of age) performance < 70%

• Left ventricular ejection fraction < 50% by echocardiogram or multi-gated acquisition (MUGA) scan * For patients unable to obtain a left ventricular ejection fraction, left ventricular shortening fraction of < 26%

• Diffusing capacity of the lungs for carbon monoxide (DLCO) (corrected/adjusted for hemoglobin) < 50%, forced expiratory volume (FEV)1 < 50% predicted, and forced vital capacity (FVC) < 50% predicted

• For patients unable to perform pulmonary function tests (PFTs) due to age or developmental delay: oxygen (O2) saturation < 92% on room air

• On supplemental oxygen

• Estimated creatinine clearance < 60 mL/minute/1.73m^2 (estimated per institutional practice)

• Dialysis dependent

• Conjugated bilirubin > 2 x ULN for age (upper limit of normal [ULN], unless attributable to Gilbert's syndrome)

• Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 4 x ULN for age, or

• Fulminant liver failure or cirrhosis

• Iron overload

•This exclusion criterion only applies to patients who are considered at risk for hepatic or cardiac iron overload. Therefore, not all patients enrolled on this protocol will undergo formal hepatic or cardiac iron assessment

• For patients >= 18 years with a history of significant transfusions defined as >= 8 packed red blood cell transfusions per year for >= 1 year or have received >= 20 packed red blood cell transfusions (lifetime cumulative) will require formal hepatic and cardiac iron measurement. In addition, patients with a prior history of hepatic or cardiac iron overload will also require formal assessment for iron overload. Patients are excluded if:

• Hepatic iron content >= 8 mg Fe/g dry weight by liver magnetic resonance imaging (MRI) using a validated methodology (such as T2 * MRI or ferriscan) or liver biopsy per institutional practice

• Cardiac iron content < 25 msec by cardiac T2 * MRI

• For patients < 18 years old with a history of significant transfusions defined as >= 8 packed red blood cell transfusions per year for >= 1 year or have received >= 20 packed red blood cell transfusions (lifetime cumulative) will require formal hepatic iron measurement. In addition, patients with a prior history of liver iron overload will also require formal assessment for iron overload. Patients are excluded if:

• Hepatic iron content >= 8 mg Fe/g dry weight by liver MRI using a validated methodology (such as T2 * MRI or ferriscan) or liver biopsy per institutional practice

• Uncontrolled bacterial infection within 1 week of study enrollment. Uncontrolled is defined as currently taking medication with no clinical improvement or progression on adequate medical treatment

• Uncontrolled viral or fungal infection within 30 days of study enrollment. Uncontrolled is defined as currently taking medication with no clinical improvement or progression on adequate medical treatment

• Positive for human immunodeficiency virus (HIV)

• Presence of clinically significant anti-donor human leukocyte antigen (HLA)-antibodies per institutional practice

• Prior solid organ transplant

• Patients with prior malignancies except resected non-melanoma skin cancer or treated cervical carcinoma in situ

• Demonstrated lack of compliance with prior medical care as determined by referring physician

• Females who are pregnant or breast-feeding

• Known hypersensitivity to treosulfan or fludarabine

• Known life-threatening reaction (i.e. anaphylaxis) to Thymoglobulin that would prohibit use for the patient as this study requires use of the Thymoglobulin preparation of anti-thymocyte globulin (ATG)

Conditions & Interventions

Interventions:
Drug: Treosulfan, Drug: Fludarabine Phosphate, Drug: Tacrolimus, Drug: Methotrexate, Biological: Lapine T-Lymphocyte Immune Globulin, Procedure: Peripheral Blood Stem Cell Transplantation, Procedure: Allogeneic Bone Marrow Transplantation, Other: Quality-of-Life Assessment

Conditions:
Bone Marrow Failure Syndrome, Congenital Amegakaryocytic Thrombocytopenia, Congenital Pure Red Cell Aplasia, Hereditary Sideroblastic Anemia, Myeloid Neoplasms With Germline GATA2 Mutation, Paroxysmal Nocturnal Hemoglobinuria, Shwachman-Diamond Syndrome

Keywords:
Bone Marrow Failure Disorders, HSCT, Treosulfan, Unrelated donor, Matched donor, mismatched donor, transplant

More Information

Contact(s): Megan Scott - bmtctn1904@emmes.com

Principal Investigator:

Phase: Phase 2

IRB Number:
System ID: NCT04965597

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