CPX-MA-1202: A Phase I/Pilot Study of CPX-351 for Children, Adolescents and Young Adults with Recurrent or Refractory Hematologic Malignancies.

PURPOSE: The purpose of this study is to test the safety of a study drug called CPX-351. This drug has been tested in adults but not yet in children and adolescents. This study tests different doses of the drug to see which dose is safer in children and adolescents.

Patients who have blood cancer are being asked to take part in this study. Blood cancers may include leukemia and lymphoma. Patients able to be in this study have already been treated with standard chemotherapy for their disease and the disease is still growing or has come back.

CPX-351 is a drug that is not yet approved by the United States Food and Drug Administration (FDA) and is only used in research studies like this one. CPX-351 is made up of two chemotherapy drugs that patients may have already received called cytarabine and daunorubicin that are now packaged together.

Another purpose of this study is to collect blood samples for special research studies. Researchers want to study how much of the CPX-351 is in the body over time. These studies are call pharmacokinetic studies or PK studies for short. PK studies require the collection of several blood samples before and after participants are given the study drug.

Study Type: Interventional
Primary Purpose: Treatment
Masking: Open Label

Detailed Description:

Cytarabine in combination with an anthracycline is a frequently used chemotherapy platform for both newly diagnosed and relapsed/refractory acute myeloid leukemia (AML) and other hematologic malignancies. Synergistic antitumor activity has been demonstrated between cytarabine and daunorubicin that is dependent upon the ratio of the drugs with the best therapeutic effect observed with a cytarabine to daunorubicin ratio of 5:1 in in vitro and in vivo models. CPX-351 is a liposomal preparation of cytarabine and daunorubicin that maintains this therapeutic drug ratio 24 hours post infusion. The altered biodistribution from encapsulation may result in a greater therapeutic effect in patients with relapsed hematologic malignancies and demonstrate greater tolerability than non-liposomal cytarabine and daunorubicin.

This is a single institution phase-I pilot study that aims to assess the pharmacokinetics, toxicity and tolerability of CPX-351 in pediatric and young adults with relapsed/refractory hematologic malignancies. Subjects will receive a single course of CPX-351 administered on Days 1, 3, and 5. The study will first open to children in a dose exploration phase, and then be available to an expanded cohort, which will be open to children and young adults once a tolerable dose has been determined.
AGEs Eligible for Study: 12 Months to 30 Years

Criteria

Inclusion Criteria:

• Age
  
  a. 12 months to 21 years at time of enrollment into dose exploration phase
  
  b. 12 months to 30 years at time of enrollment into expanded phase

• Diagnosis: Patients must have a diagnosis of a hematologic malignancy (acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or aggressive lymphoma.

• Disease Status
  
  a. Acute myeloid leukemia - patients with non-therapy related AML must be in first or greater relapse or have refractory disease to at least two courses of induction therapy.
  
  b. Acute lymphoid leukemia - patients with ALL must be in second or greater relapse or have relapsed disease refractory to re-induction therapy.
  
  c. Aggressive Lymphoma - patients must have relapsed or refractory disease for which there is no known curative therapy available. Patients must have measurable disease by CT scan.

• Performance status: Karnofsky ≥ 50% or Lansky ≥ 50.

• Prior therapy: Patients must have fully recovered from acute toxicities of prior therapy.
  
  a. Hematopoetic Stem cell transplant (HSCT): Patients who relapsed after HSCT, are eligible provided they have no evidence of active graft versus host disease (GVHD) and are at least 2 months post-transplant.
  
  b. Anthracycline exposure: Patients who have not previously had TBI (total body irradiation) must have a total previous cumulative anthracycline exposure ≤ 450 mg/m2 daunorubicin equivalents. Patients who have had prior TBI or radiation to the mediastinum must have a previous cumulative anthracycline exposure ≤ 300 mg/m2 daunorubicin equivalents.
  
  c. Cytotoxic therapy:
    
    a. AML and Lymphoma: at least 14 days must have elapsed since the completion of systemic cytotoxic therapy, with the exception of hydroxyurea.
b. ALL: patients who relapsed while receiving standard maintenance therapy do not have a waiting period. At least 14 days must have elapsed since receiving systemic cytarabine or an anthracycline/anthracenedione.

c. Intrathecal cytotoxic therapy: no waiting period is required for patients receiving intrathecal cytarabine, methotrexate and/or hydrocortisone. At least 14 days must have elapsed since receiving liposomal cytarabine in intrathecal injection.

•Organ function requirements

a. Adequate bone marrow function - platelet count ≥ 20,000/uL (may receive platelet transfusions; Hemoglobin ≥ 8 g/dL (may receive red blood cell transfusions)

b. Adequate Renal function - a maximum serum creatinine is based on age/gender. Subjects that do not meet eligibility criteria based upon serum creatinine may meet eligibility criteria based upon a 24 hour creatinine clearance or radioisotope determined GFR ≥ 70 mL/min/1.73 m2.

c. Adequate liver function - Direct bilirubin ≤ 1.5 x upper limit of normal (ULN) for age and SGPT (ALT) < 5.0 x upper limit of normal (ULN) for age and institution (unless elevation is related to leukemia involvement).

d. Adequate cardiac function - Shortening fraction of ≥ 27% by echocardiogram, or Ejection fraction of ≥ 50% by gated radionuclide study or echocardiogram.

e. Central Nervous system function - patients with seizure disorder may be enrolled if on anticonvulsants and well controlled and CNS toxicity ≤ Grade 2.

Exclusion Criteria:

•Patients with the following diagnosis are not eligible: acute promyelocytic leukemia (APML), Down Syndrome, Fanconi Anemia, acute lymphoblastic leukemia with central nervous system leukemia (CNS status 3), Wilson's disease

•Pregnant or breast-feeding women. Males and females of reproductive potential may not participate unless they have agreed to use an effective method of contraception.

•Concomitant medications

a. Growth factors- growth factors that support platelet or white cell number or function must not be administered within 7 days prior to enrollment.

b. Investigational drugs - patients currently receiving another Investigational drug are not eligible.
c. Anti-cancer agents- patients who are currently receiving other anti-cancer agents are not eligible with the exception of intrathecal cytarabine and oral hydroxyurea. Hydroxyurea must be discontinued 24 hours prior to initiation of protocol therapy.

• Infection: Patients who have an uncontrolled infection are not eligible.

• Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

• History of Wilson's disease or other copper-metabolism disorder

• Major surgery within 4 weeks of enrollment.

• Greater than 13.6 Gy prior radiation to the mediastinum

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