**SIR-MO-1101:** Pilot Study of Sirolimus Plus Multiagent Chemotherapy For Relapsed/Refractory Acute Lymphoblastic Leukemia/Lymphoma.

**PURPOSE:** The investigators want to learn about treating relapsed/refractory lymphoblastic leukemia and lymphoma with a drug called sirolimus. The investigators are using sirolimus along with other cancer drugs that are often given to patients with relapsed leukemia and lymphoma.

The main purpose of this study is to determine if sirolimus can be given safely in combination with standard drugs used to treat relapsed lymphoblastic leukemia/lymphoma.

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

**OBJECTIVES**

Primary

- To determine the rate of dose limiting toxicities
- To further determine the number of participants with adverse events to determine maximum tolerated level of sirolimus in combination with chemotherapy.

Secondary

- To measure the number of residual leukemia cells in the bone marrow.
- To measure protein phosphorylation.
- To evaluate tumor measurement by PET and/or CT Scan
- To measure changes in sirolimus plasma concentration.

**AGES ELIGIBLE FOR STUDY:** up to 30 Years

**CRITERIA**

**INCLUSION CRITERIA:**

Age: Patients must be < 30 years of age at the time of enrollment

**DIAGNOSIS**

- Acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL)
- Histology: B-precursor or T-cell
- Disease status: first or greater relapse OR primary disease refractory to two prior induction attempts
- Patients with active relapse (> 5% bone marrow blasts if ALL, detectable disease by imaging with CT and/or PET scan if LL) without prior re-induction attempt are eligible for induction (block 1) therapy followed by consolidation (block 2) therapy
• Patients with documented history of relapse who have received alternative induction therapy are eligible for consolidation (block 2) therapy.

• Patients with CNS involvement are eligible for the induction block with intensified intrathecal therapy. Those enrolling post-induction for the consolidation block must have cleared the CNS of blasts at the time of enrollment on this study. (See Appendix I for method of evaluating traumatic lumbar punctures.)

PERFORMANCE STATUS

Karnofsky >/= 50 for patients > 10 years of age OR Lansky >/= 50 for children </= 10 years of age (see Appendix II).

Oral medication -Patient must be able to consume oral medication in the form of solution or have nasogastric tube placed for administration of medication.

Prior Therapy

• Patients who relapse while receiving standard ALL maintenance chemotherapy will not be required to have a waiting period before entry onto this study.

• Patients who relapse on therapy other than standard ALL maintenance therapy must have recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study, unless deemed stable and irreversible by the investigator.

• Recovery is defined as a toxicity grade < 2 as defined by the Common Toxicity Criteria Version (CTCAE) 4.0, unless otherwise specified in the Inclusion and Exclusion criteria.

  o Cytotoxic chemotherapy: At least 7 days must have elapsed from prior cytotoxic chemotherapy regimen before initiation of treatment with sirolimus on this trial, including administration of treatment dosing of corticosteroids (physiologic replacement for adrenal insufficiency is allowed)

  o Hydroxyurea: patients with peripheral blasts may receive hydroxyurea until the first dose of cytotoxic chemotherapy for cytoreduction.

  o Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g. Neulasta) or 7 days for short-acting growth factor.

  o Biologic (anti-neoplastic) agent: At least 7 days after the last dose of a biologic agent or donor lymphocyte infusion (DLI). For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.

  o Immunotherapy: At least 6 weeks since the completion of any type of immunotherapy, e.g. tumor vaccines.

  o Monoclonal antibodies: At least 3 half-lives since prior therapy with a monoclonal antibody.
O XRT: ≥ 2 wks for local palliative XRT (small port); ≥ 24 weeks must have elapsed if prior TBI, craniospinal XRT or if ≥ 50% radiation of pelvis; ≥ 6 weeks must have elapsed if other substantial bone marrow radiation.
O Stem Cell Transplant or Rescue without TBI: No evidence of active graft vs. host disease and ≥ 12 weeks must have elapsed since transplant or stem cell infusion.

ORGAN FUNCTION REQUIREMENTS

Adequate Renal Function Defined as:
  • Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m2 or
  • A serum creatinine based on age/gender as follows:

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

Adequate Liver Function Defined as:
  • Total bilirubin ≥ 1.5 x upper limit of normal (ULN) for age
  • SGPT (ALT) ≤ 5x ULN.

Fasting serum cholesterol ≤ 300 mg/dL AND fasting triglycerides ≤ 300 mg/dL. NOTE: If one or both of these thresholds are exceeded, the patient can only be enrolled after initiation of appropriate lipid lowering medication and improvement in laboratory parameters to meet eligibility.

Fasting serum glucose ≤ 160 mg/dL. May be achieved with insulin

Adequate Cardiac Function Defined as:
  • NOTE: this applies for patients enrolling for induction block 1 only. Patients who do not meet these criteria may be eligible for block 2 therapy after alternative induction block
  • Shortening fraction of ≥ 27% by echocardiogram
  • Cumulative prior anthracycline exposure must not exceed 400 mg/m2 (each 10 mg/m2 of idarubicin/mitoxantrone should be calculated as the isotoxic equivalent of 30 mg/m2 of daunorubicin or doxorubicin)

HEMATOLOGIC PARAMETERS
  • NOTE: this applies for patients enrolling for consolidation block 2 only. Patients enrolling for induction have no blood count requirements
  • Patients enrolling for consolidation block 2 after receiving alternative re-induction not on study must have ANC ≥ 750/uL, platelets ≥ 75,000/uL and bone marrow with ≤ 5% blasts (M1).
EXCLUSION CRITERIA

Pregnancy or Breast-Feeding

- Pregnancy tests must be obtained in females of childbearing potential. Pregnant or lactating patients are ineligible for this study. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

Patients With Uncontrolled Infection

- Patients must have any active infection under control. Fungal disease must be stable for at least 2 weeks before enrollment. Patients with bacteremia must have documented negative blood cultures for > 48 hours prior to initiation of treatment.
- Patients who have a known allergy to sirolimus, FK506 (cross-reactive), or other mTOR inhibitors
- Patients who have a history of asparaginase-associated pancreatitis ARE eligible but will have asparaginase omitted from therapy. Patients who have a history of E-coli asparaginase allergy will receive Erwinia asparaginase.
- Patients with active lung disease as defined by presence of pulmonary infiltrates on screening chest x-ray or baseline room air oxygen saturation of < 93%
- Patients with a known history of hepatitis B, C, or HIV
- Patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study

Concomitant Medications

- Hematopoietic growth factor(s): Must not have received within 7 days of entry onto this study for a short-acting growth factor, or within 14 days for a long-acting growth factor
- Azoles: Due to interference with sirolimus metabolism, voriconazole, itraconazole, fluconazole, and ketoconazole should be avoided and alternative antifungal therapy initiated. If one of these agents must be given, sirolimus dosing will be decreased by 80% and trough levels monitored every other day for the first week and then weekly per protocol.
- Calcineurin inhibitors: Must be off of tacrolimus and/or cyclosporine for at least 2 weeks prior to entry on this study
- Additional medications that interact with CYP3A4: See Appendix III of the protocol for medications to be avoided while receiving sirolimus. Patients should be off these medications at least 2 weeks prior to entry on this study. If the medication is deemed essential and cannot be discontinued, sirolimus dosing will be adjusted following discussion with the study pharmacologist, Dr. Vinks, depending on the degree of expected interaction. Levels should be monitored every other day during the first week, then weekly per protocol.
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