AALL07P1: A Phase II Pilot Trial of Bortezomib (PS-341, Velcade®, IND #58,443) in Combination with Intensive Re-Induction / Therapy for Children With Relapsed Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LL) /Therapy For First Relapse

Type	Status	Age Range	Sponsors	Protocol ID
Interventional	Open	1 to 31 years	▪ COG ▪ NCI	AALL07P1

Rationale

Bortezomib may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth. Drugs used in chemotherapy work in different ways to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Giving bortezomib together with combination chemotherapy may kill more cancer cells.

Purpose

This phase II trial is studying the side effects of giving bortezomib together with combination chemotherapy and to see how well it works in treating young patients with relapsed acute lymphoblastic leukemia or lymphoblastic lymphoma.

Study Type

Interventional

Study Design

Primary Purpose – Treatment

Objectives

Primary

- To estimate the toxicity of bortezomib in combination with intensive reinduction chemotherapy in young patients with relapsed acute lymphoblastic leukemia or acute lymphoblastic lymphoma
- To estimate the second complete remission rate at the end of block 1 reinduction chemotherapy and the 4-month event-free survival of these patients

Secondary

- To assess minimal residual disease in bone marrow following completion of each block of reinduction chemotherapy

Outline

This is a multicenter study.

- **Reinduction block 1**: Patients receive cytarabine intrathecally (IT) on day 1; vincristine sulfate IV on days 1, 8, 15, and 22; doxorubicin hydrochloride IV over 15 minutes on day 1; oral prednisone twice daily on days 1-29; bortezomib IV on days 1, 4, 8, and 11; and pegaspargase intramuscularly (IM) on days 2, 8, 15, and 22. Patients with CNS-negative disease (CNS1 or CNS2) also receive methotrexate IT on days 15 and 29; patients with CNS-positive disease (CNS3) receive triple intrathecal therapy (TIT) comprising methotrexate, hydrocortisone, and cytarabine IT on days 8, 15, 22, and 29. After completion of reinduction block 1, patients with acute lymphoblastic leukemia (ALL) and M2 or M3 bone marrow proceed directly to reinduction block 2. Patients with ALL and M1 bone marrow or lymphoblastic lymphoma proceed to reinduction block 2 after blood counts recover. Patients with persistent CSF blasts after 6 doses of TIT or patients with progressive lymphoblastic lymphoma are removed from the study.
- **Reinduction block 2**: Patients receive etoposide phosphate IV over 1-2 hours on days 1-5; cyclophosphamide IV over 1 hour on days 1-5; bortezomib IV on days 1, 4, and 8; filgrastim (G-CSF) subcutaneously (SC) or IV daily beginning on day 6 and continuing until blood counts recover*; high-dose methotrexate IV on day 22; and leucovorin calcium orally or IV every 6 hours on days 23 and 24. Patients with CNS-negative disease also receive methotrexate IT on days 1 and 22; patients with CNS-positive disease receive TIT on days 1 and 22. After completion of reinduction block 2, patients proceed to reinduction block 3 immediately or when blood counts recover. Patients with disease progression are removed from the study

NOTE: *Patients do not receive G-CSF on day 8.

- **Reinduction block 3**: Patients receive cytarabine IV over 3 hours twice daily on days 1, 2, 8, and 9; L-asparaginase IM on days 2 and 9; and G-CSF SC or IV daily beginning on day 10 and continuing until blood counts recover.

After completion of study treatment, patients are followed every 6 months for 3 years and then annually for 2 years.

Ages Eligible for Study

1 Year to 31 years

Disease Characteristics

- Diagnosis of 1 of the following:
  - Pre-B acute lymphoblastic leukemia (ALL) in first early (< 36 months from diagnosis) isolated bone marrow or combined bone marrow/extramedullary relapse as documented by histology and immunophenotyping
  - T-cell ALL in first isolated bone marrow or combined relapse as documented by histology and immunophenotyping
  - T-cell lymphoblastic lymphoma in first relapse as documented by histology
    - Measurable disease as documented by clinical, radiographic, or histologic criteria
- Relapsed or refractory to conventional therapy

- No Ph+ ALL unless refractory to ≥ 1 tyrosine kinase inhibitor therapy
    - Patients who are unable to tolerate tyrosine kinase inhibitor therapy due to toxicity are eligible
- No mature B-cell ALL (i.e., sIg positive and kappa or lambda restricted positivity) with FAB L3 morphology and/or myc translocation
- No known optic nerve and/or retinal involvement
    - Patients presenting with visual disturbances should have an ophthalmological exam and, if indicated, an MRI to determine optic nerve or retinal involvement
- No extramedullary disease (i.e., isolated CNS disease or isolated testicular disease)
- No concurrent genetic syndrome (e.g., Down syndrome, Fanconi anemia, Kostmann syndrome, Shwachman syndrome, or any other known bone marrow failure syndrome)

Patient Characteristics

- Karnofsky performance status (PS) 60-100% (for patients > 16 years of age) OR Lansky PS 60-100% (for patients ≤ 16 years of age)
- Creatinine clearance or radioisotope glomerular filtration rate ≥ 70 mL/min/1.73m2 OR maximum serum creatinine based on age/gender as follows:
    - 0.4 mg/dL (for patients 1 to 5 months of age)
    - 0.5 mg/dL (for patients 6 to 11 months of age)
    - 0.6 mg/dL (for patients 1 year of age)
    - 0.8 mg/dL (for patients 2 to 5 years of age)
    - 1 mg/dL (for patients 6 to 9 years of age)
    - 1.2 mg/dL (for patients 10 to 12 years of age)
    - 1.5 mg/dL (males) or 1.4 mg/dL (females) (for patients 13 to 15 years of age)
    - 1.7 mg/dL (males) or 1.4 mg/dL (females) (for patients ≥ 16 years of age)
- Total bilirubin ≤ 1.5 times upper limit of normal (ULN) for age
- ALT < 3 times ULN for age (unless elevation due to leukemia infiltration)
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective contraception
- Shortening fraction ≥ 27% by echocardiogram OR ejection fraction ≥ 50% by gated radionuclide study
- Pulse oximetry ≥ 94% at sea level (> 90% if at high altitude)
- No evidence of dyspnea at rest or exercise intolerance
- No evidence of acute pulmonary infiltrates on chest radiograph
- No known allergy to doxorubicin, cytarabine, etoposide, etoposide phosphate, boron, mannitol, or bortezomib
- No CNS toxicity > grade 2
- Seizure disorder allowed provided patient is on anticonvulsants (e.g., benzodiazepines or gabapentin) and it is well controlled
- Able to receive asparaginase (i.e., no prior severe pancreatitis, stroke, or other toxicity)
    - Patients who initially receive asparaginase but discontinue drug due to toxicity are eligible
    - Patients with prior allergies to pegaspargase that are clinically significant are eligible provided Erwinia L-asparaginase can be substituted

Prior Concurrent Therapy

- Fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy (for patients who relapse on therapy other than standard ALL maintenance therapy)*
- No prior cumulative anthracycline exposure > 400 mg/m²
- No prior bortezomib or other proteasome inhibitors
- No prior reinduction attempts or treatment for prior extramedullary relapse
    - Patients with primary induction failure are not eligible
- At least 14 days since prior cytotoxic therapy (24 hours for hydroxyurea)
- At least 7 days since prior anticancer biologic agents or donor lymphocyte infusions
- At least 4 months since prior stem cell transplant or rescue
    - No evidence of active graft-vs-host disease (GVHD)
- No concurrent GVHD prophylaxis
- No concurrent anticonvulsants known to activate the cytochrome p450 system (e.g., phenytoin, carbamazepine, and phenobarbital)
    - Concurrent benzodiazepines or gabapentin allowed
- No concurrent corticosteroids (including steroids as antiemetics) except as treatment or prophylaxis for anaphylactic reactions OR treatment for pulmonary toxicity
- No other concurrent anticancer chemotherapy or immunomodulating agents NOTE: *Patients who relapse while receiving standard ALL maintenance chemotherapy will not be required to undergo a waiting period prior to entry onto this study.

For more information contact:

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