AAML0631: Risk Adapted Treatment of Newly Diagnosed Childhood Acute Promyelocytic Leukemia (APL) Using Arsenic Trioxide (Trisenox® IND #103331) During Consolidation/ Therapy for New Diagnosis High Risk

Type	Status	Age Range	Sponsor	Protocol ID
Interventional	Active	2 yrs to 21 yrs	- Children's Oncology Group - National Cancer Institute (NCI)	AAML0631

Outline

This is a multicenter study.

Patients are treated based on risk factor (standard-risk [WBC < 10,000/mm^3] or high-risk [WBC ≥ 10,000/mm^3]).

- Induction therapy:
  - Standard-risk: Patients receive oral tretinoin twice daily on days 1-30 and idarubicin IV over 15 minutes once on days 3, 5, and 7.
  - High-risk: Patients receive oral tretinoin twice daily on days 1-30 and idarubicin IV over 15 minutes once on days 1, 3, and 5.

Patients proceed to consolidation therapy one week later or when blood counts recover.

- Consolidation therapy:
  - Consolidation 1: Patients receive arsenic trioxide IV over 2 hours on days 1-5, 8-12, 15-19, 22-26, and 29-33 and oral tretinoin twice daily on days 1-14. Treatment repeats every 5 weeks for 2 courses, followed by a 2-week break, and then treatment repeats for 2 more courses. Beginning 1 week later or when blood counts recover, patients proceed to consolidation 2.
  - Consolidation 2: Patients receive cytarabine intrathecally (IT) on day 1, oral tretinoin twice daily on days 1-14, high-dose cytarabine IV over 3 hours every 12 hours on days 1-3, and mitoxantrone hydrochloride IV over 15-30 minutes once on days 3 and 4. Patients proceed to consolidation 3 1 week later or when blood counts recover.
  - Consolidation 3: Patients receive cytarabine IT on day 1, oral tretinoin twice daily on days 1-14, and idarubicin IV over 15 minutes once daily on days 1, 3, and 5. High-risk patients and those standard-risk patients who are positive for minimal residual disease by real-time quantitative (RQ)-PCR receive consolidation 4 one week later or when blood counts recover. All other standard-risk patients proceed to maintenance therapy.
  - Consolidation 4 (patients with high-risk cytology): Patients receive cytarabine IT on day 1, oral tretinoin twice daily on days 1-14, high-dose cytarabine IV over 3 hours every 12 hours on days 1-3, and idarubicin IV over 15 minutes once on day 4. Patients who demonstrate molecular complete remission (CR) and remain in hematological CR proceed to maintenance therapy 1 week later or when blood counts recover.
- Maintenance therapy: Patients receive cytarabine IT on day 1 (course 1 only), oral tretinoin twice daily on days 1-14, oral mercaptopurine once daily on days 1-84, oral methotrexate once on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78. Treatment repeats every 12 weeks for 9 courses.

Bone marrow or blood is collected at baseline and then periodically during the study for RQ-PCR analysis. Tumor tissue is collected at baseline for cytogenetic analysis.

After completion of study treatment, patients are followed every month for 1 year, every 3 months for 2 years, every 6 months for 2 years, and then annually for 5 years.

Objectives

Primary

- To decrease the total anthracycline dose from the best current published results in patients with standard-risk childhood acute promyelocytic leukemia (APL) while still maintaining a comparable event-free survival (EFS)

Secondary

- To assign treatment based on risk stratification by WBC at diagnosis
- To estimate the induction failure rate, toxic death rate, disease-free survival rate, and overall survival rate in both standard- and high-risk APL patients
- To monitor for cardiotonicity in an idarubicin/mitoxantrone hydrochloride-based regimen
- To document the toxicity of a traditional chemotherapy/tretinoin-based regimen combined with arsenic trioxide therapy
- To compare the EFS of children enrolled on this study with the EFS of children enrolled on CALGB-C9710 who were between the ages of 2 and 21 and did not receive arsenic trioxide
- To estimate the proportion of patients who carry a cryptic t(15;17), i.e., those who are positive for a PML-RARA fusion transcript by PCR analysis but have normal chromosomes
- To estimate the proportion of patients with variant RARA partners
- To compare the outcome of patients with only a t(15;17) with that of patients who carry a t(15;17) and other chromosomal abnormalities

Projected Accrual

- 86 patients are expected to enroll in this study

Mechanism of Action

Arsenic Trioxide (Trisenox® IND #103331) is a small-molecule arsenic compound with antineoplastic activity. The mechanism of action of arsenic trioxide is not completely understood. This agent causes damage to or degradation of the promyelocytic leukemia protein/retinoic acid receptor-alpha (PML/RARa) fusion protein; induces apoptosis in acute promyelocytic leukemia (APL) cells and in many other tumor cell types; promotes cell differentiation and suppresses cell proliferation in many different tumor cell types; and is pro-angiogenic.

Entry Criteria

Disease Characteristics:

- New clinically and morphologically confirmed diagnosis of acute promyelocytic leukemia (APL)
- If the real-time quantitative (RQ)-PCR results are known, the patient must demonstrate PML-RARA and/or RARA-PML transcripts by RQ-PCR
- Patients without evidence of APL by bone marrow morphology but with isolated myeloid sarcoma (myeloblastoma; chloroma, including leukemia cutis) are eligible provided that the t(15;17) translocation is documented on either marrow or tumor tissue by cytogenetics, FISH, or PCR prior to study enrollment (in this situation, touch preps from the tumor site can be evaluated by FISH with PML-RARA probes)

Patient Characteristics:

Age

- ≥2 years to ≤21 years

Performance Status

- There is no minimal performance status criteria for enrollment

Life Expectancy

- Not specified

Other

- Not pregnant or nursing
- Fertile patients must use effective contraception
- No pre-existing prolonged QT syndrome

Prior Concurrent Therapy:

Chemotherapy

- Prior intrathecal cytarabine prior to the diagnosis of acute promyelocytic leukemia (APL) allowed

Other

- Prior corticosteroids, hydroxyurea, and leukapheresis allowed
- No prior systemic definitive treatment for APL, including cytotoxic chemotherapy, retinoids, or arsenic

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