COG-AAML1531: Risk-stratified Therapy for Acute Myeloid Leukemia in Down Syndrome

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

PATIENT ELIGIBILITY:
Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

___1. **All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment (except studies confirming the diagnosis of Down syndrome) unless otherwise indicated. Bone marrow evaluations must be completed within 14 days prior to enrollment. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT and serum creatinine. Imaging studies, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).**

___2. Study enrollment must take place within five (5) calendar days of beginning protocol therapy. If enrollment takes place before starting therapy, the date protocol therapy is projected to start must be no later than **five (5)** calendar days after enrollment.

___3. Age at Diagnosis
Children with Down syndrome > 90 days and < 4 years of age at diagnosis of AML or Myelodysplastic Syndrome (MDS) (see Appendix III).
NOTE: The presence of myeloblasts in infants with DS during the first 90 days of life is consistent with transient myeloproliferative disease (TMD) rather than DS AML.

___4. Diagnosis
- Patients must have constitutional trisomy 21 (Down syndrome) or trisomy 21 mosaicism (by karyotype or FISH).
- Patient has one of the following:
  - Patient has previously untreated *de novo* AML and meets the criteria for AML with ≥ 20% bone marrow blasts as set out in the WHO Myeloid Neoplasm classification (see Appendix II).
    - Attempts to obtain bone marrow either by aspirate or biopsy must be made unless clinically prohibitive. In cases where it is clinically prohibitive, peripheral blood with an excess of 20% blasts and in which adequate flow cytometric and cytogenetics/FISH testing is feasible can be substituted for the marrow exam at diagnosis.
  - Patient has cytopenias and/or bone marrow blasts but does not meet the criteria for the diagnosis of AML (WHO Myeloid Neoplasm classification, see Appendix II) because of < 20% marrow blasts) and meets the criteria for a diagnosis of MDS (see Appendix III).
  - For patients who do not meet criteria for AML or MDS as outlined above. Patient has a history of Transient Myeloproliferative Disorder (which may or may not have required chemotherapy intervention), who:
    (a) is > 8 weeks since resolution of TMD with ≥ 5% blasts, OR
    (b) has an increasing blast count (≥ 5%) in serial bone marrow aspirates performed at least 4 weeks apart.

___5. Prior Therapy
Children who have previously received chemotherapy, radiation therapy or any anti-leukemic therapy are not eligible for this protocol, with the exception of cytarabine for the treatment of TMD (see Section 3.2.5.2 for timing restriction).

___6. Organ Function Requirements
There are no minimal organ function requirements for enrollment on this study.
Note: See Section 5.0 for dose adjustment in case of significant organ dysfunction. Previous cardiac repair with sufficient cardiac function as outlined in Section 5.0 is not an exclusion criteria.

EXCLUSION CRITERIA:

___1. Patients with promyelocytic leukemia (FAB M3)
___2. Prior therapy - Patients ≤ 30 days from the last dose of cytarabine used for treatment of TMD.

REQUIRED OBSERVATIONS:

All baseline studies below must be performed prior to starting protocol therapy unless otherwise indicated below.

- Physical exam, CBC with differential & platelets, twice weekly while in the hospital.
  Note: CBC with differential & platelets sent for central review should be obtained on the same day as the bone marrow aspirate.
- Creatinine, BUN, weekly while in the hospital
- Electrolytes (Ca++, Mg++, PO4), weekly while in the hospital
- AST, ALT, bilirubin (unconjugated and conjugated), weekly while in the hospital
- Height, weight
- ECG
- ECHO or MUGA
- Unilateral bone marrow aspirate (BMA); biopsy if unable to obtain a BMA
- Bone marrow baseline immunophenotype (Immunophenotyping including CD41 and/or CD61, CD33, CD34, CD14, CD7 and Gly-A is strongly recommended).
- CSF cell count and cytospin
- BMA for MRD, submit sample to Hematologics (see Section 14.1).
- Optional bone marrow sample for *GATA1* mutation analysis (see Section 14.1).
- Optional bone marrow sample for banking (see Section 14.1).

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

SPECIMEN REQUIREMENTS:

See Section 14.0.

Required and Optional Biology Specimens (Also see 14.1)

- **MRD** Required from all patients
  - Pre-treatment
- Banking of viable cells (Optional: Patient Consent Required)
  - Pre-treatment
- GATA-1 mutation (Optional: Patient Consent Required)
  - Pre-treatment

BIOLOGY REQUIREMENTS:

See Section 13.0.

CENTRAL REVIEW REQUIREMENTS:

See Section 13.0 for required slides for Central Review

TREATMENT PLAN:
EXPERIMENTAL DESIGN SCHEMA

This chart shows the treatment courses in this study.