

COG-AAML0531: A Phase III Randomized Trial of Gemtuzumab Ozogamicin (Mylotarg®) Combined with Conventional Chemotherapy for De Novo Acute Myeloid Leukemia (AML) in Children, Adolescents, and Young Adults

FAST FACTS

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. Randomization will take place at the time a patient is entered On Study via eRDE. Patients will be assigned to either Arm A (standard therapy – no GMTZ), or Arm B (experimental therapy – GMTZ given).
- ___ 2. Enrolled Down syndrome patients equal to or over 4 years of age will be non-randomly assigned to Arm A – standard therapy.
- ___ 3. **Timing** - Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 5 calendar days after the date of study enrollment. Administration of IT chemotherapy is permitted before enrollment when administered as part of an initial diagnosis lumbar puncture.
- ___ 4. **Specimens for cytogenetics analysis are required, must be obtained prior to therapy initiation, and it is strongly recommended that they be sent to a COG-approved institutional cytogenetics laboratory** (see Section 15.2). A listing of these laboratories may be found on the COG website as well as methods of attaining COG approval for local cytogenetics laboratories without COG approval. Because the chromosome analysis results should be finalized by the end of Induction Course I, and will be used for subsequent risk stratification and in order to guide therapy by Day 28 of a patient's enrollment, **the case should be sent to the appropriate reviewer by Day 14 (see Appendix II)**. Results of cytogenetics are not required to be completed prior to enrollment, but samples must be collected prior to therapy initiation and submitted to a cytogenetics laboratory.
- ___ 5. **Age**
 - Children \geq 1 month and children and young adults $<$ 30 years of age with newly diagnosed AML may be treated on this protocol.
 - Infants $<$ 1 month of age with AML may be given supportive care until it is clear that the leukemia is not regressing, i.e., the disappearance of peripheral blasts and the normalization of peripheral blood counts; infants $<$ 1 month with progressive disease are eligible for study entry.
 - Patients with Down syndrome greater than or equal to age 4 years will be eligible.
- ___ 6. **Diagnosis**
 - Patients with previously untreated primary AML who meet the customary criteria for AML with \geq 20% bone marrow blasts as set out in the WHO Myeloid Neoplasm classification (see Appendix IV). 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.
 - Patients with cytopenias and bone marrow blasts who do not meet the customary criteria for the diagnosis of AML (patients with $<$ 20% blasts) are eligible if they have a karyotypic abnormality characteristic of de novo AML ($t(8;21)(q22;q22)$, $inv(16)(p13q22)$ or $t(16;16)(p13;q22)$ or $11q23$ abnormalities), or if they have the unequivocal presence of megakaryoblasts, as set out in the WHO Myeloid Neoplasm classification (see Appendix IV).
 - Patients with isolated myeloid sarcoma (myeloblastoma; chloroma, including leukemia cutis) are eligible regardless of the results outlined in Sections 3.2.2.1 and 3.2.2.2, as set out in the WHO Myeloid Neoplasm classification (see Appendix IV).
- ___ 7. There is no minimal performance status criteria for enrollment.
- ___ 8. **Prior Therapy** - Children who have previously received chemotherapy or radiation therapy or any antileukemic therapy are not eligible for this protocol. Exceptions include corticosteroids (any route), and IT cytarabine given at diagnosis.
- ___ 9. Patients of childbearing potential must have a negative pregnancy test and agree to use an effective birth control method. Lactating patients must agree not to nurse a child while on this trial.

- ___ 10. Children with documented myelodysplastic syndrome (MDS) (CMML, RA, RAEB, RARS, etc.) are only eligible if they present with karyotypic abnormalities of de novo AML ($t(8;21)(q22;q22)$, $inv(16)(p13q22)$ or $t(16;16)(p13;q22)$ or $11q23$ abnormalities), or if they have the unequivocal presence of megakaryoblasts (see Section 3.2.2.2).
- ___ 11. Those with juvenile myelomonocytic leukemia (JMML) are **not** eligible.
- ___ 12. Patients with Fanconi anemia (FA), Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome are **not** eligible.
- ___ 13. Patients with promyelocytic leukemia (FAB M3) are **not** eligible.
- ___ 14. Patients with secondary or treatment related AML are **not** eligible.

INDUCTION STRATIFICATION FACTORS:

RISK CATEGORY STRATIFICATION

AAML0531 is utilizing a stratification for relapse risk to guide both therapy and analyses. The section below outlines and defines the three risk categories – High, Intermediate, and Low. These classifications should be made no later than the beginning of Induction II.

Low Risk Disease

These patients are defined by cytogenetics only as having the presence of either $inv(16)/t(16;16)$, or $t(8;21)$ regardless of the adverse characteristics monosomy 7 or $-5/5q-$. These patients do NOT receive SCT in first remission, regardless of whether a matched related donor is available and regardless of whether they additionally have the High risk feature of >15% blasts after Induction I. However, those with FLT3 high ITD-AR will be moved to the High risk group. Patients with Down syndrome will follow therapy as outlined for Low risk patients.

High Risk Disease

All patients in this category will receive SCT, if possible, after Intensification I. These patients are defined by either the presence of specific adverse cytogenetics (-7 , or $-5/5q-$), the presence of a high FLT3 ITD-AR (> 0.4), or persistence of significant leukemic cell concentrations in the marrow exam ($>15\%$) after the first course of Induction chemotherapy. These latter patients will be defined as having persistent disease but will not be considered a Primary Induction failure. Primary Induction Failure will be designated if a patient has $\geq 5\%$ marrow blasts found on the marrow exam after Induction II. Note that patients with High risk features with concomitant favorable cytogenetics ($inv(16)/t(16;16)$, $t(8;21)$) will be considered Low risk and will not receive SCT with the single exception that FLT3 high ITD-AR patients remain in the High risk group. Also, High risk patients for whom no suitable alternative donor can be found should continue with their assigned chemotherapy regimen.

Intermediate Risk Disease

All patients who have neither Low nor High risk disease as defined above will be designated as having Intermediate risk disease. Those patients in whom cytogenetics were unable to be performed will be included in this risk group. Patients with a MFD will receive a SCT. Intermediate risk patients for whom MFD is not available should continue with their assigned chemotherapy regimen.

REQUIRED OBSERVATIONS:

Required Clinical, Laboratory and Disease Evaluations Plus Optional Research

- History
- Physical Exam (Ht, Wt, BSA, VS)
- CBC
- BUN/Creatinine
- AST/ALT, bili (direct and total)
- Echo or MUGA /EKG
- High Resolution HLA/DNA typing: patient, parents, siblings ¹
- Biopsy and CT/MRI of chloroma *
- BMA/Biopsy or BMA/clot section ^{2#}
- LP-CSF for cell count, cytopsin
- BMA cytogenetics and FISH ^{##}
- Pregnancy Test, if applicable
- BMA for FLT-3 (3-5 mL purple top)*
 - * In order to provide uniform FLT3-ITD mutation analysis that is used for risk based therapy, all FLT3 testing will be performed as part of the protocol therapy at a single site through NIH funding. FLT3-ITD testing and allelic ratio determination will be performed by the Molecular Oncology Laboratory at Seattle Cancer Care Alliance (SCCA) **free of charge to the patient.** Please see protocol for details.

Below are Optional Research Sample Time-Points

- BMA for MRD [#]
- Peripheral Blood for Gene Polymorphisms [^]
- Bone marrow or peripheral blood sample sent for GATA1 analysis, gene expression and in vitro pharmacology studies ^{DS#}

Recommended Clinical, Laboratory and Disease Evaluations

- Urinalysis
 - Electrolytes, Ca, Phos
 - LDH
 - Uric Acid
 - Quant. Igs
 - CMV serology
 - Varicella serology
 - HSV serology
 - CXR
 - PT/PTT, fib, FDP or d-dimers
 - Cr Clearance or GFR
- 1 All AML patients will have HLA-typing at diagnosis except those with obvious DS. If an HLA-identical sibling is not identified at presentation, then high resolution typing of the patient should be performed at HLA-A, B, C and DRB1.
- * For patients with granulocytic sarcomas only.
- # For consenting patients: extra marrow (or peripheral blood) is to be collected for optional biology studies in green top tube (preservative free heparin) at time of disease status evaluation. See Section 16.1 for send out guidelines
- ^ For consenting patients: utilize purple top tube. See Section 16.2.2 & 16.1 for send out guidelines.
- DS This sampling of GATA1 is restricted to Down syndrome patients only. Per the instructions in Section 16.4.
- ## See Cytogenetics Sections 14.0 and 15.0 for submission guidelines.
- 2 If it is unadvisable clinically to perform a BM at diagnosis or relapse, the use of peripheral blood may be substituted in cases where there are adequate numbers of blasts to conclusively make the diagnosis of AML. In these cases, peripheral blood should also be sent for all the biological studies requested at diagnosis or relapse (see Section 15.1.4).

TREATMENT PLAN:

See 4.0.

TOXICITIES AND DOSAGE MODIFICATIONS:

See 5.0.

SPECIMEN REQUIREMENTS:

Required Materials for Pathology Review

Submit slides, institutional reports and transmittal forms to the Biopathology Center as described below.

These samples should be submitted within 7-14 days of the procedure.

All Patients at the time of Disease Diagnosis Evaluation and Diagnosis of Refractory Disease or Relapse

The following materials are required*:

1. A completed pathology report
2. A peripheral blood smear (Wright-Giemsa stained)
3. A concurrent complete blood count including white blood cell differential (manual or automated)
4. A bone marrow aspirate smear (Wright-Giemsa stained)
5. A bone marrow clot section OR core biopsy (H&E stained)
6. 4 unstained slides on clot section or core biopsy (preferably on charged slides)

THESE MATERIALS WILL BE RETAINED BY COG AND WILL NOT BE RETURNED.

RECOMMENDED ADDITIONAL MATERIALS:

1. Additional aspirate smears (stained and/or unstained)
2. Cytochemical stains (myeloperoxidase, non-specific esterase, PAS)
3. Immunohistochemical stains (ex. CD34, CD117, myeloperoxidase)
4. Tissue blocks (tissue blocks will be returned promptly on conclusion of study)

*Patients can be included without these specimens on approval of the Chair or Vice-chair of the study.

This approval will be contingent on the adequacy of alternate materials (e.g., peripheral blood) for performance of all tissue based techniques for the study.

Biopathology Center Shipping Address:

Biopathology Center – AAML0531
Children's Hospital
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: 614-722-2894
Fax: 614-722-2897

As of January 23rd, 2009, samples for FLT3-ITD testing on AAML0531 should be sent to Seattle Cancer Care Alliance (SCCA) at the address indicated below.

Molecular Oncology
Seattle Cancer Care Alliance
1100 Fairview Avenue North, Rm. D2-281
Seattle, WA 98109
Phone: 206.667.2592
Fax: 206.667.6092

The Lab hours are Mon-Fri 8 am – 4:30 pm closed on weekends and holidays. For Saturday deliveries, laboratory needs be informed of the shipment. Please see the Molecular Oncology Requisition Form for details regarding sample collection, handling and shipping, and include this form with every request for specimen testing.

Please allow 5-7 business days for samples to be processed. Results will be communicated by fax.

OPTIONAL BIOLOGY REQUIREMENTS:

- 3-7 ml of bone marrow in a green top tube (substitute blood if bone marrow unobtainable).
- 5 ml peripheral blood in a purple top.