Gemtuzumab Ozogamicin in Children and Adolescents with de novo Acute Myeloid Leukemia (AML) Improves Event-free Survival by Reducing Relapse Risk – Results from the Randomized Phase III Children's Oncology Group Trial, AAML0531

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DOI: 10.1200/JCO.2014.55.3628

Activated: 08/14/06
Closed: June 15, 2010

Version Date: 07/19/11
Amendment #3

CHILDREN'S ONCOLOGY GROUP

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

A Groupwide Phase III Study

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progenitors in only 19/24 samples. A bipotent progenitor was affected in a subset of patients, as evidenced by the presence of FLT3/ITD in both granulocyte-macrophage colony-forming unit (CFU-GM) and erythroid burst-forming unit (BFU-E) colonies. Those patients in whom CD34+/CD33- precursors harbored the FLT3/ITD had worse clinical outcome; actuarial event-free survival (EFS) at 4 years from study entry for those patients with and without FLT/ITD detection in CD34+/CD33- progenitors was 11% vs. 100%, respectively (P = .002). This study suggests that FLT3/ITD involvement in CD34+/CD33- precursors is heterogeneous and that presence of the mutation in the less mature progenitor population may be associated with disease resistance. Based on this data we will evaluate the diagnostic specimens from patients with molecular aberrations identified previously for the early progenitor involvement and correlate early progenitor involvement with clinical outcome.

2.11.1 Correlation of Minimal Residual Disease (MRD) by Flow Cytometry with Clinical Outcome

Many studies of ALL have demonstrated the prognostic importance of early response to therapy.[124] Although response may be measured by morphologic examination of the bone marrow, minimal residual disease studies using flow cytometric detection of aberrant immunophenotypes or polymerase chain reaction (PCR) assays have proved to be even more useful.[125,126] In AML, patients with ≤ 5% morphologic blasts on Day 15 of therapy have an improved outcome, compared to patients with > 5% blasts.[127] As in ALL, measurement of MRD levels using flow cytometry is also predictive of relapse. In one of the first studies reported, Sievers et al. demonstrated that detectable leukemic blasts at the time of morphologic remission were predictive of more rapid relapse.[128]

In comparison with historical features associated with leukemic relapse, Sievers et al. have recently shown in a prospective study of 252 AML patients that flow cytometric evidence of leukemia after the initiation of therapy was the most powerful independent prognostic factor associated with poor outcome. In a time-dependent multivariate analyses that controlled for allogeneic marrow transplantation, variable intervals between sample submission, age, sex, white blood cell count at diagnosis, presence of splenomegaly or hepatomegaly, and presence of > 15% blasts in the marrow after the first course of induction, patients harboring occult leukemia were 4.8 times more likely to relapse (95% CI = 2.8 to 8.4, P < .0001) and 3.1 times more likely to die (95% CI; 1.9 to 5.1, P < .0001) than those without detectable leukemia by flow cytometry. Overall survival at 3 years was 41% vs. 69% for patients with and without occult leukemia, respectively (P = .006).[129] Based on these results, we are evaluating a second-generation flow cytometric assay to increase the proportion of high-risk patients identified during periods of clinical remission. Although first generation 3-color multi-dimensional flow (MDF) was able to successfully distinguish a portion of patients who subsequently relapsed, the assay failed to detect occult leukemia in approximately half of all patients who ultimately had leukemic recurrence. For this reason, we will evaluate a more sensitive, yet highly specific 4-color flow cytometric assay to assess for occult leukemia in prospective COG AML studies. Improved assay sensitivity should enable identification of a larger portion of patients who will subsequently relapse. In this manner, treatment for such high-risk patients could be intensified to prevent deaths from leukemic relapse.

3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the eRDE system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN).*

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

3.1.2 IRB Approval

Local IRB/REB approval of this study is to be entered into the Online IRB Submission System by each site. In addition, the official signed copy of the IRB approval document must be faxed to the Group Operations Center (GOC) at: (626) 445-6715. Once IRB/REB approval documentation is received by COG, the institution will have access to the RDE enrollment screens within the next business day.

3.1.3 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the eRDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG website.

3.1.4 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.

3.1.4.1 Central Venous Access

It is recommended that all patients have a double lumen central venous access line placed prior to the beginning of therapy.

3.1.4.2 Cytogenetics

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.

3.1.4.3 FLT3 Testing

Specimens for FLT3 mutation analysis with Allelic Ratio testing are required, must be obtained prior to therapy initiation, and must be sent to laboratories that have a validated FLT3 mutation analysis, specifically with Allelic Ratio testing. A list of validated molecular genetics laboratories is posted on the COG website and will be updated periodically. The result of the FLT3 mutation analysis will be used for risk assignment. All patients that do not have adequate specimens submitted will receive a risk assignment based upon other criteria. See Section 14 for specimen collection and shipping details.

Results of FLT3 testing are not required to be completed prior to enrollment, but samples must be collected prior to therapy initiation and submitted to a validated molecular genetics laboratory.

3.1.5 Clarification of Consent for Diagnostic Bone Marrow Samples

It is recommended that patients initially provide consent for drawing and shipping extra bone marrow/peripheral blood. This may spare the child from having a second procedure. Investigators may use the sample one page consent for bone marrow sampling provided with this protocol or may use their own institutional consent for diagnostic bone marrow sampling. If an institutional consent is used, it should include within it that extra samples of bone marrow will be obtained and shipped for potential research studies should the diagnosis of AML be made.

Once the diagnosis of acute leukemia is confirmed and AML is diagnosed, separate consent for enrollment on this therapeutic study must be completed prior to enrollment onto AAML0531. Permission to use the extra bone marrow samples for the performance of research studies will be obtained within this therapeutic study consent. The consent that pertains to the bone marrow sampling should permit the immediate shipment of the samples to the AML reference laboratory. This will maximize the viability of the samples. The samples will only be kept if the patient enrolls on COG AAML0531 and only if the patient's family has approved their use as identified in the therapeutic study consent. In other words, the samples for those who do not enroll on AAML0531 for any reason will be destroyed. If, at any time, in the future, the patient wants banked tissue destroyed, the COG tissue bank must be notified immediately by the local institution and the RDE system will be updated and forwarded to the appropriate Reference Laboratory, who will destroy the tissue. Patients must be informed that their tissue can only be prospectively destroyed; that is, any research studies that have already been conducted prior to the date that they decided they wanted their tissue destroyed cannot be amended.

3.1.6 Bilingual Services

To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

3.1.7 Randomization

Randomization will take place at the time a patient is entered On Study. Patients will be assigned to either Arm A (standard therapy – no GMTZ), or Arm B (experimental therapy – GMTZ given).

3.1.7.1

Enrolled Down syndrome patients equal to or over 4 years of age will be non-randomly assigned to Arm A – standard therapy.

3.2 Patient Criteria

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.

3.2.1 Age

- Children ≥ 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.

3.2.2 Diagnosis

3.2.2.1
Patients with previously untreated primary AML who meet the customary criteria for AML with ≥ 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.

3.2.2.2
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).

3.2.2.3
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).

3.2.3 Performance Level
There is no minimal performance status criteria for enrollment.

3.2.4 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.

3.2.5 Concomitant Medications Restrictions
None

3.2.6 Other Restrictions

3.2.6.1
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.

3.2.6.2
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).

3.2.6.3
Those with juvenile myelomonocytic leukemia (JMML) are **not** eligible.

3.2.6.4
Patients with Fanconi anemia (FA), Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome are **not** eligible.

3.2.6.5
Patients with promyelocytic leukemia (FAB M3) are **not** eligible.

3.2.6.6
Patients with secondary or treatment related AML are **not** eligible.

3.2.7 Regulatory

3.2.7.1
All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.7.2
All institutional, FDA, and NCI requirements for human studies must be met.

3.3 Definitions

3.3.1
INITIAL WBC: The first WBC at the treating COG institution.

3.3.2
INITIAL PLATELET COUNT: The first platelet count at the treating COG institution, or the count before transfusion of platelets if transfused prior to arrival.

3.3.3
INITIAL HEMOGLOBIN: The first hemoglobin at the treating COG institution, or the hemoglobin prior to intravenous fluid or red cell transfusions, whichever occurred first.

3.3.4
CNS LEUKEMIA AT DIAGNOSIS:

3.3.4.1
CNS disease at diagnosis is defined as:

Any number of blasts on a cytospin prep in an atraumatic (< 100 RBCs) lumbar puncture.

Blasts in a traumatic tap in which the WBC/RBC ratio in the CSF is twice that in the peripheral blood.

Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

Radiographic evidence of an intracranial, intradural mass consistent with a chloroma.

3.3.4.2
METHOD OF EVALUATING INITIAL TRAUMATIC LUMBAR PUNCTURES:

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains blasts, the following algorithm should be used to diagnose CNS disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} \quad > 2X \quad \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF blasts, whose CSF WBC/RBC is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis. Example: CSF WBC = 60/μL; CSF RBC = 1500/μL; blood WBC = 46000/μL; blood RBC = 3 X 10^6/μL:

$$\frac{60}{1500} = \mathbf{0.04} \quad \mathbf{> 2X} \quad \frac{46000}{3 \times 10^6} = \mathbf{0.015}$$

3.3.5
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.

3.3.5.1 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.

3.3.5.2 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 ≥ 5% marrow blasts found on the marrow exam after Induction II.

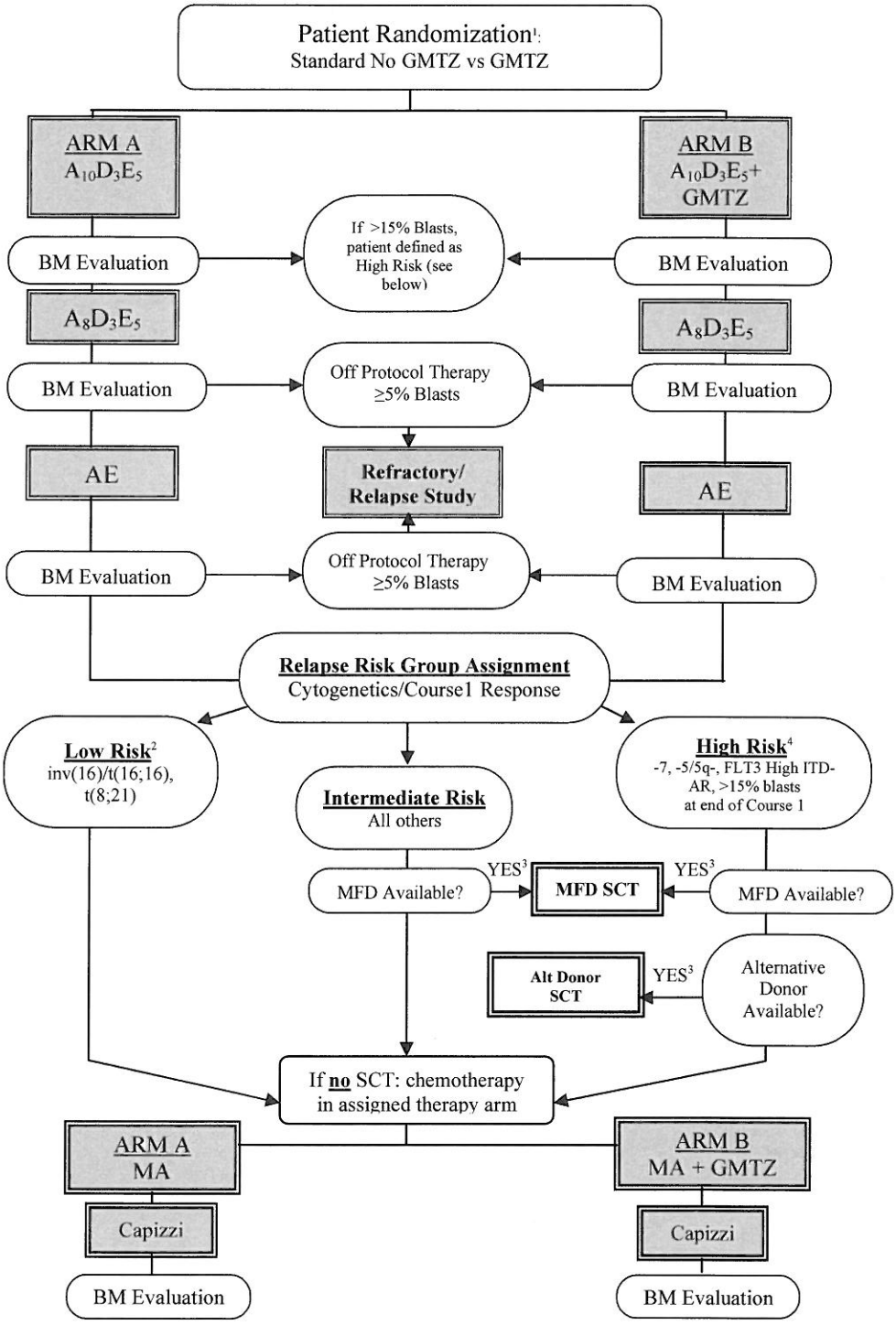
Note that patients with High risk features with concomitant favorable cytogenetics *(inv(16)/t(16;16), t(8;21))* will be considered Low risk and will not receive SCT with the single exception that FLT3 high ITD-AR patients remain in the High risk group. Also, High risk patients for whom no suitable alternative donor can be found should continue with their assigned chemotherapy regimen.

3.3.5.3 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.

3.4 Pre-Enrollment Baseline Diagnostic Requirements

See Section 7.0 for all required and recommended baseline pre-enrollment evaluations.

EXPERIMENTAL DESIGN SCHEMA



1. Down syndrome patients non-randomly assigned to "No GMTZ" standard arm; Down syndrome patients do not receive MFD SCT in CR1 and should continue on to Course 4 chemotherapy.
2. Low Risk patients: inv(16)/t(16;16), t(8;21) do not receive MFD SCT in CR1 and should continue on to chemotherapy (regardless of Course 1 remission status). FLT3 High ITD-AR supersedes Low Risk cytogenetics.
3. BM exam required prior to SCT.
4. High Risk (-7, -5/5q-, FLT3 High ITD-AR, & Course 1 persistent disease) patients go to MFD SCT if available, otherwise to Alt Donor SCT. (inv(16)/t(16;16), t(8;21), and DS patients will not be classified as High Risk regardless of their remission status after Course 1.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary objective

To compare the event free survival (EFS) and overall survival (OS) of *de novo* acute myeloid leukemia (AML) patients randomized between the best current chemotherapy with or without gemtuzumab ozogamicin (GMTZ).

1.2 Secondary objectives

1.2.1
To compare the remission induction rates after two courses of the best current induction chemotherapy utilizing cytarabine (10 days), daunomycin (3 days), and etoposide (5 days) (ADE (10+3+5)) with or without GMTZ.

1.2.2
For those patients who are eligible for a HLA-matched family donor (MFD) stem cell transplant (SCT) by virtue of their risk classification, to compare disease free survival (DFS) and OS between patients assigned to MFD SCT if a MFD is available, or to chemotherapy if a MFD is not available.

1.2.3
To determine the outcome of patients with Down syndrome who are 4 years of age or older at diagnosis and treated on this regimen without GMTZ.

1.2.4
To compare the EFS and OS of *de novo* AML patients randomized between the best current chemotherapy with or without GMTZ censoring MFD SCT recipients.

1.2.5
To determine the prevalence and prognostic significance of molecular abnormalities of KIT, CEBPα and MLL-PTD genes in pediatric AML.

1.2.6
To determine the leukemic involvement of hematopoietic early progenitor and its role in defining response to therapy.

1.2.7
To assess the ability of a second generation flow cytometric assay to predict patients at high risk for relapse during periods of clinical remission.

1.2.8
To examine whether GMTZ significantly improves EFS and OS in patients with higher CD33 concentrations/intensity.

1.2.9
To examine whether GMTZ significantly improves CR, EFS and OS in each of the cytogenetic risk groups (High, Intermediate, and Low risk) identified in prior MRC trials.

1.2.10
To utilize florescence in situ hybridization (FISH) analysis to identify variant patterns among subgroups of patients who demonstrate the same G-banded chromosomal abnormality (e.g., inv(16)/t(16;16), t(8;21), 11q23 abnormality) and to determine whether these variant patterns account for the heterogeneity of responses to therapy.

4.0 TREATMENT PLAN

4.1 General Information (See Appendix I for Supportive Care Guidelines)

4.1.1 Treatment of Metabolic Derangement and Toxicity

Prior to the initiation of therapy, establish the best possible control of coagulopathy, metabolic derangement, and institute therapy for fever and/or infection if appropriate.

4.1.2 Central Venous Access

It is recommended that all patients have a double lumen central venous access line placed prior to the beginning of therapy.

4.1.3 Metabolic Support

If the risk of tumor lysis is present, patients should receive vigorous hydration with an IV solution containing sodium bicarbonate ($NaHCO_3$) (to alkalinize the urine) and no potassium, and begin allopurinol 10 mg/kg/day PO (maximum 300 mg/day) before therapy begins. Observation or rasburicase (the latter without alkalinization) may also be used as clinically appropriate.

4.1.4 Patient Size Modifications

This dosing modification for infants and small children is based upon a 1989 CCG study in children with AML that found a greater than expected toxic induction mortality rate for children less than three years of age.[130] Doses of chemotherapeutic agents were modified for children ≤ 3 years resulting in fewer deaths, less toxicity and improved survival.

Chemotherapy doses will be modified only for patients with a BSA < 0.6 m^2. **For patients with BSA < 0.6 m^2, chemotherapy will be dosed in mg/kg as specified in the treatment plan.**

No chemotherapy dose modification will be made for obese patients except in stem cell transplant. These dose modifications are described in Section 4.14.3.

Age and weight adjusted busulfan dosing guidelines are found in Section 4.14.5.1.

4.2 Dose Modifications for CNS Disease

4.2.1 Intrathecal Chemotherapy

In patients who are CNS negative (**no** blasts on a cytospin prep in an atraumatic (< 100 RBCs) lumbar puncture; see additional criteria in Section 3.3.4), intrathecal cytarabine will be given on Day 1 of Induction I (ADE 10+3+5), Day 1 of Induction II (ADE 8+3+5), and Intensification I and II (AE and MA). No intrathecal medication will be administered during Capizzi II (Intensification III).

The first dose of intrathecal cytarabine may be given at the time of the diagnostic marrow, but there must be no uncertainty about the diagnosis. A separate institutional consent form for the administration of cytarabine IT therapy must have been signed and must accompany the signed protocol consent form. **No other chemotherapy medication may be administered prior to obtaining a signed and documented IRB-approved protocol consent form. If IT cytarabine is given prior to the signing of the protocol consent form, then consider it as the Day 1 IT cytarabine dose and do not give additional IT cytarabine on Day 1 of protocol therapy.**

Schema

Day –10	Begin phenytoin (see Section 4.14.4)
Day –9	Busulfan q 6 hours x 4 doses (see age-based dosing Section 4.14.5.1) with 1st dose pharmacokinetics (see Section 16.5).
Day –8 to Day –6	Busulfan q 6 hours x 12 doses with targeted dose-adjustment based on PK results.
Day –5 to Day –2	Cyclophosphamide daily x 4 days
Day –3 to -1	ATGAM (Equine ATG) 30 mg/kg
Day –1	Begin Cyclosporine A
Day 0	Bone Marrow Infusion
Day 1	Methotrexate 15 mg/m^2/dose IV
Day 3	Methotrexate 10 mg/m^2/dose IV
Day 6	Methotrexate 10 mg/m^2/dose IV
Day 11	Methotrexate 10 mg/m^2/dose IV

4.15.4
See Sections 4.14.4 through 4.14.10 with the following additions or exceptions.

4.15.5 ATGAM
ATGAM is utilized in addition to busulfan and cyclophosphamide in patients with alternative donors as follows:
ATGAM 30 mg/kg/dose IV over 6-8 hours on Days -3, -2, -1. Premedication will be given prior to infusion with diphenhydramine 1 mg/kg/dose, max 50 mg (or comparable anti-histamine) and methylprednisone 1 mg/kg/dose. Premedications may be repeated or increased as needed to control allergic reactions, chills or fever. Patients who are unable to tolerate the equine product may receive Thymoglobulin 2.5 mg/kg/day.

4.15.6 Cyclosporine A (CSA)
Follow the guidelines in Section 4.14.8.2 with the exception that tapering of CSA does not begin until Day 100.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Hepatic Toxicity

5.1.1
If the ALT or AST are > 10 x normal, attempts should be made to identify the cause and notify the Study Chair. In most cases, the therapy will proceed without modification.

5.1.2
If the direct bilirubin is > 3 mg/dL, notify the Study Chair. In some cases it may be necessary to proceed if the bilirubin elevation is a result of the leukemia itself. If the elevated direct bilirubin is not a result of the leukemia, and is between 2 and 3 mg/dL, give 50% of the calculated dose of daunorubicin and etoposide. If the direct bilirubin is between 3 and 5 mg/dL give 25% of the daunorubicin and etoposide doses, and notify the Study Chair. If the direct bilirubin is > 5 mg/dL hold the daunorubicin and etoposide and notify the Study Chair. Full dose of these agents may resume when the direct bilirubin has fallen to < 1.2 mg/dL. In severe liver dysfunction, the half-life of mitoxantrone is prolonged and the AUC may be more than 3-fold that of patients with normal hepatic function. However, there are no available dose adjustment guidelines in the literature. Therefore, follow similar dose reductions of mitoxantrone as outlined above for daunorubicin based upon bilirubin levels. For patients with a bilirubin > 3 mg/dL notify the study chair. For all cases in which the direct bilirubin is elevated at the point in time that the next course is to begin, consider delaying the course for one week to determine whether the direct bilirubin falls to an acceptable level.

5.1.3 Sinusoidal Obstruction Syndrome (SOS, formerly VOD) of the Liver
SOS is a known toxicity of GMTZ. No specific predisposing factor is known that may identify the patient at risk.

5.1.3.1 Criteria for the diagnosis of SOS of the liver
For the purposes of reporting toxicity, the following definition for SOS will be used:

1) Weight gain of more than 10% baseline, and
2) Right upper quadrant pain or tender hepatomegaly, and
3) Total bilirubin 2 mg/dL or greater, and
4) Edema or ascites.

Reversal of portal venous blood flow by ultrasound or pathologic confirmation by liver biopsy are not required for the diagnosis but may be done in support of the clinical diagnosis and/or the evaluation of other diagnostic possibilities. Ultrasound may also be used to assess the severity and course of the patient's SOS.

5.1.3.2 Therapy Modification for SOS
Please notify the Study Chair or Vice-Chair of any episode of SOS as an adverse event (AE) and hold protocol chemotherapy and **discontinue further use of GMTZ.** Resume therapy as per the modification guidelines in Section 5.1.2.

5.2 Left Ventricular Cardiac Function Toxicity

5.2.1
Daunorubicin and mitoxantrone will be withheld if there is significant evidence of cardiac disease by echocardiogram or MUGA (shortening fraction < 27%). Do not re-start these drugs if withheld for this reason. Prolongation of the corrected QT interval (QT_c) may be an early indicator of cardiac toxicity, particularly if used serially during and after therapy. Cardiac examination with Echo (or MUGA) is required prior to the start of Induction I and II (daunorubicin containing courses) and Intensification II (Mitoxantrone containing course), and at the end of protocol therapy. See Table 7.5 for long-term follow-up.

5.3 Neurologic Toxicity

5.3.1
Patients with ≥ Grade 3 neurotoxicity from high dose cytarabine should not receive further high dose cytarabine. The most common neurotoxicity is an acute cerebellar syndrome that may manifest itself as ataxia, nystagmus, dysarthria, or dysmetria. However, seizures and encephalopathy have also occurred following therapy with high dose cytarabine. **If neurotoxicity of ≥ Grade 3 occurs during or following therapy, the patient will go Off Protocol Therapy for toxicity.**

5.4 Renal Toxicity

5.4.1
Patients with nephrotoxicity secondary to antibiotics, or antifungals, may have prolonged excretion of cytarabine leading to more severe marrow and extramedullary toxicity. Patients with a serum creatinine > 2 mg/dL or > 2 x normal for age should be hydrated orally or intravenously. Following hydration, the patient must have a creatinine clearance ≥ 60 mL/min/1.73m² as measured preferably by a nuclear GFR Scan, timed urine collection for creatinine clearance, or calculated by the Schwartz formula before proceeding with HD cytarabine therapy (doses of 1 gm/m^2 or greater). If the CrCl is abnormal (< 60 mL/min/1.73m^2) then high dose cytarabine should be reduced from twice daily to once daily dosing, at the same previously prescribed doses (e.g., 50% daily dose reduction). With this approach, previous research has shown the prevention of subsequent neurotoxicity in recipients of high dose cytarabine in the face of renal insufficiency.[131]

In patients with impaired renal function, the following **initial** dose modification of etoposide should be considered based on measured creatinine clearance: for CrCl > 60 mL/min give full dose, for CrCl of 15-60 mL/min give 75% of the dose (25% dose reduction). For CrCl < 15 mL/min notify the Study Chair. (Please note: For dose adjustment in renal dysfunction for children, use the "corrected" value for creatinine clearance measured in mL/min/1.73 m^2, which 'corrects' that value for the standardized values of CL_{Cr} in adults, measured in mL/min. The "corrected" value is loosely interpreted as being equivalent to creatinine clearance measured in an adult patient). **Subsequent doses** should be based on patient tolerance and clinical effect.

A serum/plasma creatinine calculation using the Schwartz formula (Schwartz et al. J. Peds, 106:522, 1985):

Estimated Creatinine Clearance (in mL/min/1.73 m^2)** = **(*k*)(L)/Pcr**

Where L = child's length in cm
Pcr = plasma (or serum) creatinine (in mg/dL)

k Values =	
0.33	low birth weight infant
0.45	term infant
0.55	child
0.55	adolescent female
0.70	adolescent male

**The conversion formula for serum/plasma creatinine when reported in μMol/L units:
(*k* • ht)/(sCr in μMol/L / 88.4)

5.5 Methotrexate Dose Adjustments

5.5.1
Every attempt possible should be made to administer methotrexate as prescribed since dose reduction and omission have been associated with an increased incidence of acute GVHD. Not every impairment in renal function and not every increase in third space fluid are contraindications to the use of methotrexate. It may be advantageous to give methotrexate, possibly at a reduced dose (75%-50%), and offer rescue with leucovorin. Several studies have shown that this will reduce toxicity without increasing the risk of GVHD.

Any questionable situation must be discussed with the Transplant Study Committee Representative and serum methotrexate levels determined. If at 48 hours the methotrexate level falls in the toxic range, consult the nomogram shown in Figure 3 for leucovorin rescue and adjustment of subsequent dosages. Leucovorin should be continued until the methotrexate levels are < 0.1 micromolar.

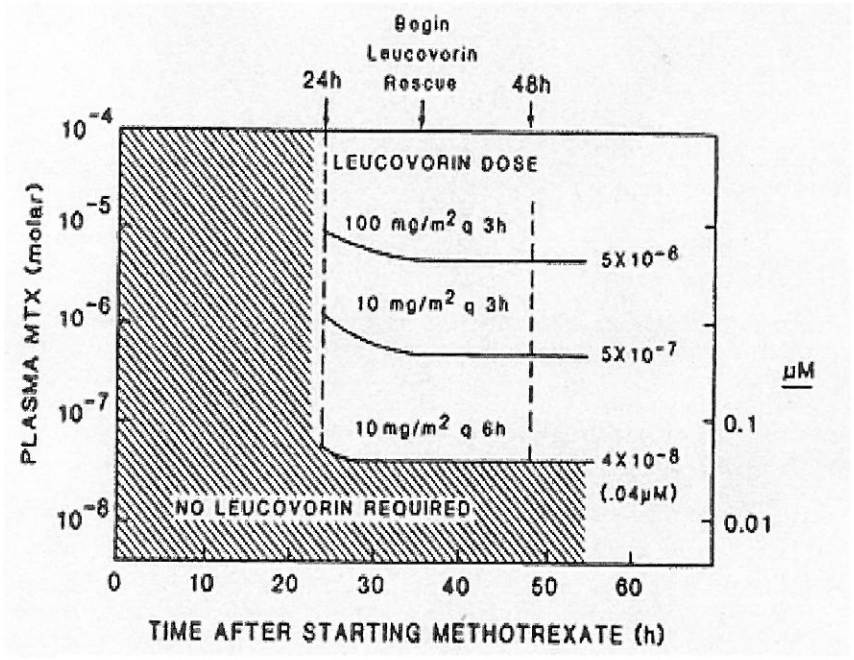


Figure 3. MTX plasma levels and leucovorin "rescue."

5.6 Cyclosporine Dose Modifications

Weekly CSA levels will be obtained in patients with a rising BUN, creatinine, and pancytopenia. Doses should be adjusted to keep CSA trough levels between 150 – 250 ng/mL.

5.7 Allergy to Etoposide

Etoposide allergic reactions may be managed with pre-medications such as diphenhydramine 1 mg/kg IV, ranitidine 1 mg/kg IV, hydrocortisone 1-4 mg/kg IV, and by slowing the rate of the infusion. For those reactions which are unable to be controlled with pre-medication and the slowing of the rate of etoposide infusion, etoposide phosphate may be substituted in the same dose and at the same rate. Pre-medication for etoposide phosphate is recommended.

5.8 Asparaginase [E.coli, Pegaspargase (PEG-Asparaginase) or Erwinia]

Allergy

Local Reactions (inflammation at injection site, swelling): Continue E.coli administration in the presence of Grade 1 allergy as defined by CTCAE (transient flushing or rash; drug fever < 38^0C). Premedication with antihistamines to decrease the risk of overt allergy symptoms is strongly discouraged since anti-histamine use may mask the appearance of systemic allergy. Systemic allergy is associated with the presence of asparaginase neutralizing antibodies, which render asparaginase therapy ineffective.

Anaphylaxis/Systemic Allergic reactions: Discontinue asparaginase if the patient develops a systemic allergic reaction (urticaria, wheezing, laryngospasm, hypotension, etc). Should an allergy be diagnosed after the first dose given on Day 2 during Intensification Course 3, then the dose due on Day 9 should not be administered.

Coagulopathy: If symptomatic, omit Day 9 asparaginase in Intensification Course 3 and consider factor replacement (FFP, cryoprecipitate, factor VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.

Hyperbilirubinemia: L-asparaginase may need to be withheld in patients with an elevated bilirubin, since asparaginase has been associated with hepatic toxicity. There are no specific guidelines available.

Hyperglycemia: Do not modify dose. Treat hyperglycemia as medically indicated.

Hyperlipidemia: Do not modify dose.

Ketoacidosis: Hold asparaginase until blood glucose can be regulated with insulin.

Pancreatitis (Grade 2-4): Discontinue asparaginase in the presence of hemorrhagic pancreatitis or severe pancreatitis (abdominal pain > 72 hours and > Grade 3 amylase elevation (> 2.0 x ULN). In the case of mild pancreatitis after Day 2 of Intensification Course 3, Day 9 asparaginase may be given only if symptoms and signs subside, and amylase levels return to normal. Severe pancreatitis is a contraindication to additional asparaginase administration.

Thrombosis: Discontinue asparaginase and treat with appropriate antithrombotic therapy, as indicated. Do not withhold dose for abnormal laboratory findings without clinical correlate. For significant thrombosis, not line related, consider evaluation for inherited predisposition to thrombosis.

CNS Events (bleed, thrombosis or infarction): Discontinue asparaginase. Treat with FFP, factors or anticoagulation as appropriate. Consider evaluation for inherited predisposition to thrombosis.

6.0 DRUG INFORMATION

See the consent document for toxicities. All other information is available on the COG website in the manual titled "Drug Information for Commercial Agents used by the Children's Oncology Group" at: https://members.childrensoncologygroup.org/prot/reference_materials.asp under **Standard Sections for Protocols.**

b) Relapse of any site following remission.
c) Refusal of further protocol therapy by patient/parent/guardian.
d) Completion of planned therapy.
e) Physician determines it is in patient's best interest.
f) Refractory CNS leukemia following 6 doses of IT cytarabine therapy.
g) Grade 3 or greater neurotoxicity from HD cytarabine or
h) Other intolerable or unacceptable toxicity.
i) Development of a 2nd malignancy.

Please contact the Study Chair prior to taking patient off protocol therapy.

Patients who are off protocol therapy are to be followed until they meet the criteria for off study (see below). Follow-up data will be required unless consent was withdrawn.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence)*
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of study's closure to accrual.
f) Patient is determined to be ineligible.

*For subsequent studies with a significant interval between enrollment and beginning of therapy (i.e., studies involving stem cell transplant where there will be an attempt to identify an adequate donor), the patient will come off AAML0531 at the time when therapy is initiated on the subsequent study (and not at time of enrollment onto that study).

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

The patients with de novo AML will be randomized at study entry to receive GMTZ or no-GMTZ. All patients at least 4 years of age with Down syndrome will be assigned to receive the no-GMTZ arm.

9.2 Patient Accrual and Expected Duration of Trial

This study will accrue patients for 3½ years or until there are 1000 eligible patients, whichever occurs later, with a follow-up of 1 year after the last patient is randomized. Based on previous accrual rates and allowing for initially slow recruitment with study opening, we expect in 3½ years to accrue approximately 1000 patients with de novo AML and 12 patients over the age of 4 with Down syndrome. Biologic studies will be performed on all patients.

9.3 Statistical Analysis Methods

9.3.1 Study Endpoints

The primary outcome measures are EFS, defined as the time from on study to induction failure, relapse, or death; OS from on-study. Secondary endpoints include the remission rate after two courses of therapy (Induction I and II); DFS, defined as the time from the end of Course 3 (Intensification I) to death or relapse; the proportion of patients dying during the first three courses of therapy; time to marrow recovery; and frequency of toxicities, including infectious complications.

9.3.2 Analysis Plan

The Kaplan-Meier method will be used to calculate estimates of OS, EFS, and DFS.[132] Analysis of OS, EFS, DFS, remission induction rate, and toxicities of Down syndrome patients will be performed