Cytarabine plus Continuous Infusion Daunorubicin Induction Therapy for Adults with Acute Myeloid Leukemia; A Feasibility Study with Cardiac MRI Monitoring

Wake Forest Baptist Comprehensive Cancer Center (WFBCCC)

WFBCCC 22616

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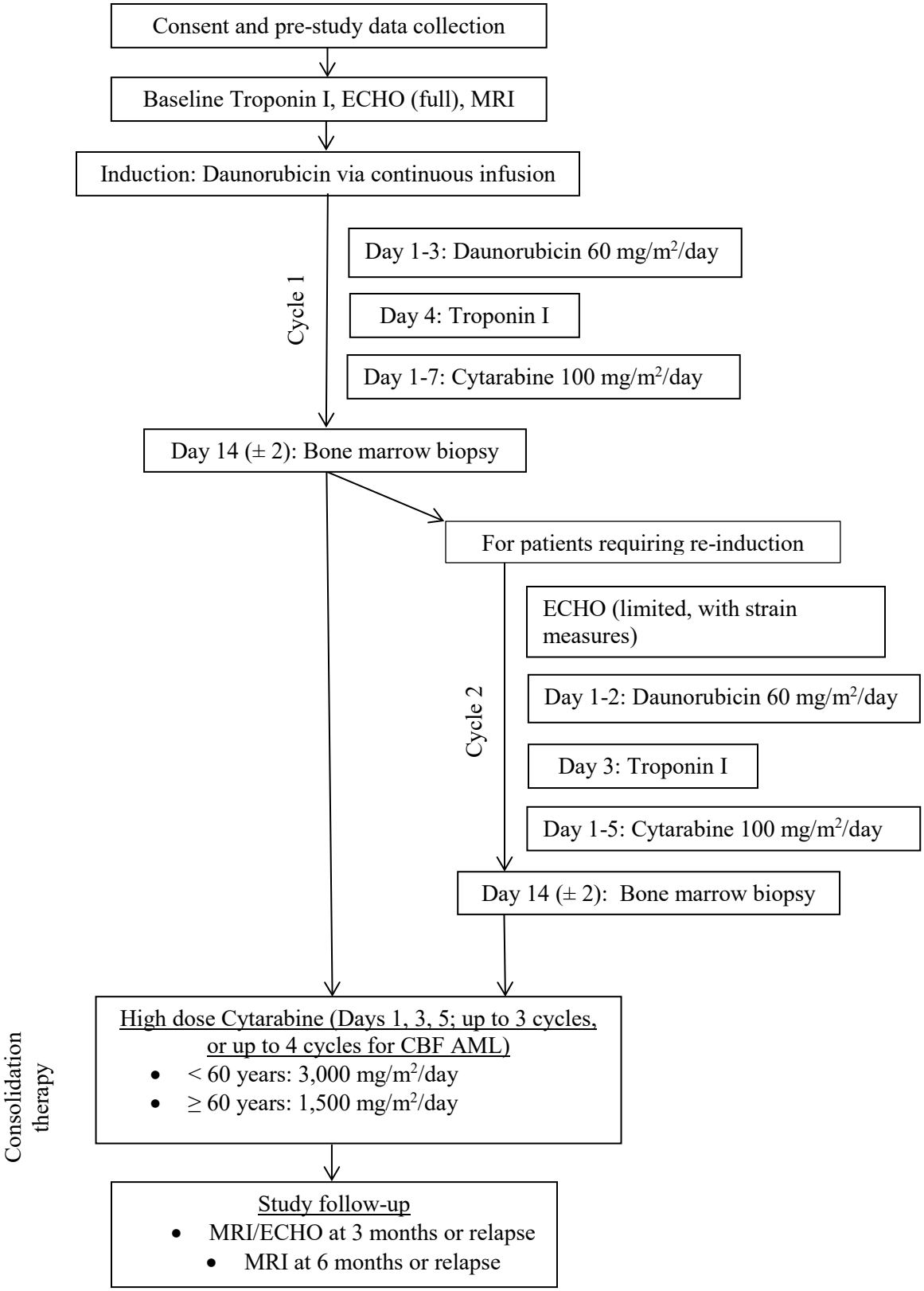
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1.0 Introduction and Background

It is estimated that 19,950 people will be diagnosed with acute myeloid leukemia (AML) and 10,430 will die from it in the United States in 2016.[1] Standard induction therapy for patients with good performance status consists of a 7+3 regimen of cytarabine 100-200 mg/m^2 continuous infusion x 7 days with an anthracycline, i.e. daunorubicin 60-90 mg/m^2 (45-90 mg/m^2 for patients ≥60 years or idarubicin 12 mg/m^2) x 3 days.[2] While advances in treatment have resulted in substantially improved complete remission (CR) rates, with 60% to 70% of adults expected to attain CR status following appropriate induction therapy, only slightly more than 25% (about 45% of those who attain CR) can be expected to survive 3 or more years.

1.1 Chemotherapy-induced cardiotoxicity

Along with myelosuppression, cardiac effects are the key dose-limiting toxicities of daunorubicin and other drugs in the anthracyclines class. Treatment with daunorubicin can result in arrhythmias and cardiomyopathy, with a maximum total (lifetime) dose of 500-600 mg/m^2 recommended because of cumulative cardiotoxicity. Currently there is no reliable method of predicting patients at increased risk for developing cardiotoxicity. Transthoracic echocardiography is used most widely to measure cardiac function and volume because of its availability, anatomic and prognostic validation, and lack of ionizing radiation.[3-5] Furthermore, when cardiac chambers contract in a uniform and symmetric pattern, a close correlation is found between echocardiographic and angiographic volume measurements.[6] Limitations of echocardiography include difficulty in assessing the apex and right ventricle. In addition, assumptions regarding the geometry of the LV (as a prolate ellipsoid) are used to estimate ventricular volumes and mass. MRI acquires tomographic 2D or 3D images of the entire heart. Volumetric assessment of the LV is independent of geometric assumptions, noninvasive, and free of exposure to contrast agents or ionizing radiation. MRI is considered superior to other imaging techniques because of its capability for high-resolution measurements of anatomy and function of the LV.[7] Cardiac MRI was successfully implemented in the Multi-Ethnic Study of Atherosclerosis (MESA), sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health.[8]

1.2 Daunorubicin administration

Previous studies in patients with advanced breast and ovarian cancer and metastatic soft tissue sarcoma have examined cardiotoxicity outcomes with bolus versus continuous infusion administration of anthracyclines and found a decreased risk with continuous infusion.[9-11] A Southwest Oncology Group study in AML patients included infusional daunorubicin and cytarabine with and without cyclosporin and concluded that infusional daunorubicin did not significantly alter the toxicity profile or efficacy of the standard 7+3 regimen, although, this was not the main objective of the study.[12]

There is limited but sufficient evidence to suggest that daunorubicin administered as a continuous infusion rather than bolus in the standard 7+3 regimen would provide a reduced risk of cardiotoxic effects with at least similar response rates. As such, this study aims to assess the safety and feasibility of administering daunorubicin as a continuous infusion in patients undergoing induction therapy for newly diagnosed AML.

We will assess clinical outcomes under the proposed regimen, as well as examine the use of cardiac MRI in identifying cardiac toxicity.

2.0 Objectives

2.1 Primary Objectives

2.1.1 To assess the safety (at 3 months) and feasibility of administering daunorubicin as continuous infusion under the proposed treatment regimen.

2.2 Secondary Objectives

2.2.1 To assess the safety (at 6 months) of administering daunorubicin as continuous infusion under the proposed treatment regimen.

2.2.2 To assess treatment outcomes (including CR and CRi) in patients with AML under the proposed treatment regimen.

2.2.3 To compare the concordance between MRI and ECHO in identifying cardiac toxicity, i.e. a reduction in LVEF of ≥10% and EF≤50% compared to baseline LVEF.

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Patients must have morphologically confirmed newly diagnosed acute myelogenous leukemia (AML) with blood or bone marrow disease. Patients with only extramedullary disease in the absence of bone marrow or blood involvement are eligible. Note: This protocol uses WHO diagnostic criteria for AML. Patients with acute promyelocytic leukemia (APL, FAB, M3) or blastic transformation of chronic myelogenous leukemia (CML) are not eligible.

3.1.2 ≥ 18 years of age.

3.1.3 ECOG performance status 0-3.

3.1.4 Patients with ECHO EF ≥ 45% within 28 days prior to registration.

3.1.5 Because of the teratogenic potential of the drugs used in this study, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.6 Ability to understand and the willingness to sign an IRB-approved informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have received prior induction chemotherapy for AML or MDS. Temporary prior measures such as apheresis or hydroxyurea are allowed. Patients who have received a limited and short-term exposure of ATRA (all trans retinoic acid) while AML-M3 (Acute Promyelocytic Leukemia) was being ruled out, and which has been discontinued, will be eligible.

3.2.2 Patients receiving any other investigational agents.

3.2.3 Patients with prolonged QTc interval (> 500 msec) determined by EKG within 28 days prior to registration.

3.2.4 Patients not suitable for cardiac MRI. Contraindications include:

- Intracranial metal, pacemakers, defibrillators, functioning neurostimulator devices, or other implanted electronic devices
- Ferromagnetic cerebral aneurysm clips, or other intraorbital/intracranial metal
- Allergy to Gadolinium or other severe drug allergies
- Claustrophobia
- Congestive heart failure (NYHA class III or IV)
- Significant valvular disease, or significant pulmonary disease requiring supplemental oxygen therapy

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to daunorubicin or cytarabine.

3.2.6 Patients with documented CNS involvement.

3.2.7 Patients who are known to be HIV+ may be eligible providing they meet all of the following additional criteria within 28 days prior to registration:

- CD4 cells ≥ 500/mm3
- Viral load of < 50 copies HIV mRNA/mm3 if on cART or < 25,000 copies HIV mRNA if not on cART
- No zidovudine or stavudine as part of cART

Patients who are HIV+ and do not meet all of these criteria are not eligible for this study.

3.2.8 Patients with other uncontrolled intercurrent illness or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects with drugs used in this study. Because there is an unknown but potential risk for adverse events in nursing infants

secondary to treatment of the mother with the drugs used in this study, breastfeeding should be discontinued prior to beginning treatment.

3.3 Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study.

The study consent form will also be provided in Spanish for Spanish-speaking participants. Based on WFBCCC population estimates, we expect approximately 44% of participants to be women. Translating this to our sample size estimate of 40, we plan to enroll at least 18 women. Similarly, we expect approximately 3% of study participants to be Hispanic/Latino (N=1). We plan to enroll at least 11% Black or African American (N=4), 0% American Indian/Alaska Native (N=0), .006% Asian (N=1). Should we not meet or exceed these estimates, the PI will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in these target populations.

4.0 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be registered with the WFBCCC Protocol Registrar or entered into ORIS Screening Log within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix B)
2. Complete the Protocol Registration Form (Appendix A)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   Contact Information:
   Protocol Registrar PHONE (336) 713-6767
   Protocol Registrar FAX (336) 713-6772
   Protocol Registrar E-MAIL (registra@wakehealth.edu)
   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

5.0 Study Outcomes

5.1 Primary Outcomes

5.1.1 Cardiac toxicity(see 2.2.3), as measured by MRI (ejection fraction [EF], left ventricular end diastolic volume [LVEDV], left ventricular end systolic volume [LVESV], T1/T2 mapping and myocardial strain) measures and ECHO (EF, myocardial strain, LVEDV, LVESV, ESV, mitral inflow E, A, E' and A') measures. Cardiac toxicity is defined as reduction in LVEF of ≥10% compared to baseline LVEF and EF≤50% on the follow-up scan. This assessment will be performed using both an ECHO and MRI measure. In addition, the primary outcome will be assessed at the 3 month follow-up (or relapse) visit.

5.1.2 Other unexpected toxicities (exclude hematologic and infectious) ≥ grade 3, as measured by CTCAE v 4.0

5.1.3 Feasibility, as measured by ability to administer continuous infusion daunorubicin and complete required study assessments with limited deviation from the proposed regimen (as defined in section 8.2)

5.2 Secondary Outcomes

5.2.1 Cardiac toxicity(see 2.2.2), as measured by MRI (ejection fraction [EF], left ventricular end diastolic volume [LVEDV], left ventricular end systolic volume [LVESV], T1/T2 mapping and myocardial strain) measures and ECHO (EF, myocardial strain, LVEDV, LVESV, ESV, mitral inflow E, A, E' and A') measures. Cardiac toxicity is defined as reduction in LVEF of ≥10% compared to baseline LVEF and EF≤50% on the follow-up scan. This assessment will be performed using both an ECHO and MRI measure. In addition, these secondary outcomes will be assessed at the 6 month follow-up (or relapse) visit

5.2.2 Treatment outcomes (such as overall response rate) stratified by age (≥60, < 60) and ECOG (0-2, 3): Overall response rate (CR + CRi); Induction death rate; Presence of persistent leukemia; Disease-free survival (for those who achieve remission)

5.2.3 Measures of ECHO and MRI derived measures of EF, myocardial strain, LVEDV and LVESV.

6.0 Treatment Plan

	Study entry[a]	INDUCTION: (up to 2 Cycles) *At each treatment*	INDUCTION CYCLE 1 *Additional Activities*		INDUCTION CYCLE 2 (**if needed as indicated by bone marrow aspirate and biopsy) *Additional Activities*			CONSOLIDATION: (up to 4 Cycles for CBF AML) *At each treatment*	Post-treatment	Follow-up or relapse	
			Day 4	Day 14 (+/- 2 days)	Prior	Day 3	Day 14 (+/- 2 days)			3 mos.	6 mos
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X										
Physical exam	X										
Vital signs	X	X						X			
Height, Weight, M^2	X										
Performance Status	X										
Bone marrow aspirate & biopsy[b]	X			X[b]			X[b]		X[b]		
CBC w/diff, platelets	X	X						X	X		
Serum chemistry[c]	X[d]	X						X			
Troponin I (Appendix E)	X[d]		X[e]			X[e]					
B-HCG[f]	X										
ECHO (Appendix E)	X[h]				X[g]					X[g]	
MRI without contrast (Appendix E)	X									X	X
Adverse event evaluation	X	X	X	X	X	X	X	X	X	X	X

[a] Completed within 28 days prior to registration unless otherwise indicated.
[b] On day 14 (±2 days) of Induction Cycles 1 and 2, at recovery to confirm response, and at completion of all treatment, then as clinically indicated.
[c] Total bilirubin, BUN, creatinine, SGOT[AST], SGPT[ALT]
[d] Draw after consent signed and prior to day 1 treatment; results not required to start treatment.
[e] On day 4 of treatment of Induction Cycle 1, and on day 3 of Induction Cycle 2 for those with persistent leukemia.
[f] Serum pregnancy test (women of childbearing potential).
[g] Limited ECHO with strain measures
[h] Full 3D ECHO

6.1 Treatment Administration

Treatment will be administered on an inpatient basis. Reported adverse events and potential risks are described in Section 9. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Agent	Dose	Route	Schedule	Cycle Length
Induction				
Cytarabine	100 mg/m^2/day	IV infusion	Days 1-7	14 days
Daunorubicin	60 mg/m^2/day	IV infusion	Days 1-3	
Re-induction (if needed)				
Cytarabine	100 mg/m^2/day	IV infusion	Days 1-5	14 days
Daunorubicin	60 mg/m^2/day	IV infusion	Days 1-2	
Consolidation (up to 3 cycles, or up to 4 cycles for CBF AML)				
Cytarabine	<60 yrs: 3,000 mg/m^2/day ≥ 60 yrs: 1,500 mg/m^2/day	IV infusion over 3 hours, every 12 hours	Days 1,3,5	≥ 28 days

Induction: This study regimen will follow the standard 7+3 regimen of cytarabine and daunorubicin, with the modification of daunorubicin administered as continuous infusion rather than bolus. Baseline troponin I, full 3D ECHO, and MRI without contrast will be performed prior to treatment.

For troponin determination, the study will use either the TnI-Ultra™ assay, Siemens, Munich Germany or the Beckman Coulter Access 2 AccuTnI+3 assay for detection of troponin I. While the assays are comparable, every effort will be made to test all samples on the current Institutional standard troponin I testing platform (TnI-Ultra assay, Siemens). If the TnI-Ultra assay becomes unavailable either because of changing Institutional standards or product availability the Beckman Coulter Access 2 AccuTnI+3 assay will be utilized. The brand of assay and results will be recorded for each test on the Cardiac Function Worksheet.

Patients will have a bone marrow aspirate and biopsy on day 14 (±2 days).

Re-induction: A second induction course may be given if the day 14 bone marrow aspirate and biopsy shows bone marrow cellularity as ≥10% and >5% leukemic blasts. Those requiring re-induction will undergo a limited ECHO with strain measures prior to treatment. This abbreviated cycle will consist of cytarabine on days 1-5 and daunorubicin on days 1 and 2, with a troponin I measure on day 3 and a bone marrow biopsy on day 14 (±2 days). Patients not achieving a remission after 2 induction attempts will be removed from study.

Patients without bone marrow involvement at diagnosis will receive a second induction course if they have not cleared their soft tissue disease by day 14 (± 2 days).

If cellularity is <10% on day 14, a repeat bone marrow biopsy should be obtained as clinically indicated. Treatment response will be evaluated once ANC >1,000 /μL and platelets ≥100,000/μL, but no later than day 42. If peripheral blood counts are inadequate (ANC<1,000/μL, platelets<100,000/μL) at the time of this bone marrow aspirate and biopsy, a repeat bone marrow aspirate and biopsy must be obtained to document complete remission at the time of peripheral blood count recovery (ANC≥1,000/μL, platelets≥100,000/μL) if > 1 week after "day 42" bone marrow study.

Physicians should consider earlier bone marrow exams in patients whose peripheral blood counts are not recovering or recovering sluggishly, as well as in patients whose day 14 bone marrow was suspicious for residual leukemia.

Consolidation: Patients in remission will receive high-dose cytarabine (days 1, 3, and 5) consolidation therapy for up to 3 cycles (except in the case of toxicity or receipt of stem cell transplant). Patients with core-binding factor (CBF) AML may receive 4 cycles of consolidation therapy. Therapy should be started as soon as possible (and within 14 days) after recovery from induction/re-induction therapy.

6.1.1 Allogeneic Stem Cell Transplant

Patients with intermediate and high-risk disease by cytogenetics and/or molecular studies should be considered for allogeneic transplant while in first remission. The transplantation, including donor selection, will not be guided by this protocol but will be at the discretion of the treating physician.

6.1.2 Positive for FLT-3

Patients found to be positive for FLT-3 may have midostaurin added to induction and consolidation per approved indications

6.2 Imaging exams

Upon enrollment, subjects will be scheduled for the echocardiogram, cardiac MRI exam and clinic visit for labwork. For the Ultrasound portion of the study, the subject will go to the Clinical Ultrasound lab. After arrival at the ultrasound lab, the subject will be positioned on a scanning bed with ECG leads attached. Then an ultrasound transducer will be placed on the subject's chest and pictures will be taken of the heart using three-dimensional imaging and spectral Doppler techniques. The total time of the ultrasound testing will be 45 minutes. The MRI exam will be performed in the CMR suite where they will be placed supine on the CMR table and ECG leads and respiratory gating bellows applied. CMR scans will be performed on a 1.5 Tesla GE CVi scanner with a phased array surface coil applied around the chest to optimize signal to noise. All images will be acquired using a fast gradient echo technique, with the repetition time (TR) and echo time (TE) based on the R-R interval of the subject. Multi-slice coronal, gradient echo sequences will be used to obtain scout images of the chest and locate the left ventricle. After locating the LV a series of steady state free precession, short axis views will be

acquired perpendicular to the left ventricle covering from the base to the apex; imaging parameters were 32cm field of view, 35˚ flip angle, 8mm slice thickness, 2mm inter-slice space, and a 256X128 matrix. These scans will incorporate a temporal resolution of 40msec in order to identify end-systole for the determinations of LV volumes, EF, and mass. This protocol will be identical to that implemented in CCWFU 98998 and the Multi-Ethnic Study of Atherosclerosis.[13]

6.3 Analysis of MRI images

For LV mass, volume, and EF determinations, calculations will be performed according to widely published and currently accepted techniques that are in current use at or institution in single and multi-center trials. The epi- and endocardial border of each slice from the multi automated drawing program, and assessments will be calculated by summation (Simpson's rule). Basal slices will be reviewed in cine format to resolve structures for inclusion (the aortic outflow tract) or exclusion (left atrium and mitral leaflets) from the mass, volume, and EF measurements.

6.4 General Concomitant Medication and Supportive Care Guidelines

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., as clinically indicated. Anti-inflammatory or narcotic analgesics may be offered as needed. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

6.5 Duration of Therapy

Treatment under this protocol may continue until one of the following criteria applies:

- Allogeneic stem cell transplant,
- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.6 Duration of Follow Up

Patients will have an MRI without contrast and full/limited ECHO at 3 months or relapse, whichever occurs first. Patients still on protocol at 6 months post-treatment will have an MRI without contrast only.

Patients will be followed for a minimum of 30 days after the last study drug is administered or until death, whichever occurs first, for adverse events monitoring. Patients removed from the study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients will be followed by phone call every 3 months for monitoring survival endpoints.

7.0 Dose Modifications

Induction: no dose reductions allowed.

Re-induction: Dose reductions may be allowed in the setting of hepatotoxicity as follows:

- For SGPT/SGOT 150-300 U/L **OR** bilirubin 1.5-3.0 mg/dL, reduce daunorubicin dose to 45 mg/m^2/day.
- For SGPT/SGOT > 300 U/L **OR** bilirubin > 3.0-5.0 mg/dL, reduce daunorubicin dose to 30 mg/m^2/day.

Consolidation: No dose reductions allowed for Cycle 1 except in the instance of renal dysfunction, as follows:

- For creatinine greater than 2 mg/dL or calculated creatinine clearance of < 50 mL/min, decrease cytarabine dose to 1,000 mg/m^2/dose.
- For creatinine greater than 3 mg/dL or calculated creatinine clearance of < 30 mL/min, change cytarabine to 400 mg/m^2/day IV infusion over 24 hours daily for 5 days.

For consolidation cycles beyond Cycle 1, doses of cytarabine may be reduced by 750 mg/m^2/day for the following reasons:

- Grade 3-4 non-hematologic toxicity
- Severe life-threatening infection

If toxicity persists, cytarabine dose may be reduced by an additional 750 mg/m^2/day.

8.0 Measurement of Effect

8.1 Antitumor Effect

Response and progression will be evaluated in this study criteria defined by Cheson et al.[14] (see Appendix D).

8.2 Definitions

- Study Regime: Completion of the critical study regime tasks will be tracked by research staff and recorded as “Yes” or “No” in Appendix E, The Cardiac Function form. The tasks that should be recorded in this manner are the following:
- The daunorubicin infusion (Induction):
    - if this is not completed in 72 hours +/- 1, record as “No”,
    - If the infusion in completed within these parameters record “yes”.
        - If “No”, record the total infusion amount and time taken to administer.

- ECHO (at pre-induction visit, *post-treatment (pre-discharge), 3 month follow-up or relapse):
  - Record “Yes” or “No” if the patient completes or does not complete the ECHO at each visit.
  - *indicates an additional assessment for those individuals requiring a second cycle of Induction therapy
- MRI (at pre-induction visit, 3 month follow-up or relapse, at 6 month follow-up or relapse):
  - Record “Yes” or “No” if the patient completes or does not complete the MRI at each visit.
- Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with daunorubicin.
- Persistent leukemia: Patients not achieving a remission after 2 induction attempts; these patients will be removed from the study.
- Disease-free survival: calculated for patients who achieve CR and measured from the date of CR until relapse from CR or death. Observation is censored at the date of last follow-up for patients last known to be alive without report of relapse.
- Time to death: calculated from date of study registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

9.0 Adverse Events List and Reporting Requirements

9.1 Adverse event list for daunorubicin

Acute myelosuppression is the dose limiting side effect, with the greatest effect on the granulocytic series. In addition, daunorubicin causes alopecia, and nausea and vomiting in a significant number of patients treated. Extravasation of daunorubicin can cause severe local tissue necrosis. There is increased potential for cumulative-dose-related cardiomyopathy with congestive heart failure.

9.2 Adverse event list for cytarabine (CYTOSAR)

Conventional Dose Therapy Table 1 - Adverse Reactions (with conventional dose therapy): The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency. Frequencies are defined as: Very common (>10%), Common (>1%, ≤10%), Uncommon (>0.1%, ≤1%), Rare (>0.01%, ≤0.1%), and Frequency not known (cannot be estimated from available data).	
Blood and Lymphatic System Disorders:	
Very common	Bone marrow failure, thrombocytopenia, anaemia, anaemia megaloblastic, leukopenia, reticulocyte count decreased
Frequency not known	Bleeding (all sites)
Cardiac Disorders:	
Frequency not known	Pericarditis
Eye Disorders:	
Frequency not known	Conjunctivitis[a]

Gastrointestinal Disorders:	
Very common	Stomatitis, mouth ulceration, anal ulcer, anal inflammation, diarrhea, vomiting, nausea, abdominal pain
Frequency not known	Bowel necrosis, Pancreatitis, oesophageal ulcer, oesophagitis
General Disorders and Administration Site Conditions:	
Very common	Pyrexia
Frequency not known	Chest pain, injection site reaction[b]
Hepatobiliary Disorders:	
Very common	Hepatic function abnormal
Frequency not known	Jaundice
Infections and Infestations:	
Very common	Sepsis, pneumonia, infection[c]
Frequency not known	Injection site cellulitis
Immune System Disorders:	
Frequency not known	Anaphylactic reaction, allergic oedema
Investigations:	
Very common	Biopsy bone marrow abnormal, blood smear test abnormal
Metabolism and Nutrition Disorders:	
Frequency not known	Decreased appetite
Musculoskeletal, Connective Tissue and Bone Disorders:	
Very common	Cytarabine syndrome
Nervous System Disorders:	
Frequency not known	Neurotoxicity, neuritis, dizziness, headache
Renal and Urinary Disorders:	
Frequency not known	Renal impairment, urinary retention
Respiratory, Thoracic and Mediastinal Disorders:	
Frequency not known	Dyspnoea, oropharyngeal pain

[a] may occur with rash and may be hemorrhagic with high dose therapy

[b] pain and inflammation at subcutaneous injection site

[c] may be mild, but can be severe and at times fatal

High Dose Therapy

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of CYTOSAR(cytarabine) has been reported following high dose schedules (2.0 g to 3.0 g/m^2 given every 12 hours for 12 doses). **Table 2: Adverse Reactions (with High Dose Therapy):** The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency. Frequencies are defined as: Very common (>10%), Common (>1%, ≤10%), Uncommon (>0.1%, ≤1%), Rare (>0.01%, ≤0.1%), and Frequency not known (cannot be estimated from available data).

Cardiac Disorders:	
Frequency not known	Cardiomyopathy[a]

Eye Disorders:	
Very common	Corneal disorder
Frequency not known	hemorrhagic conjunctivitis[b]
Gastrointestinal Disorders:	
Common	Necrotizing colitis
Frequency not known	Gastrointestinal necrosis, gastrointestinal ulcer, pneumatosis intestinalis, peritonitis
Hepatobiliary Disorders:	
Frequency not known	Liver injury, hyperbilirubinaemia
Infections and Infestations:	
Very common	Sepsis
Frequency not known	Liver abscess
Nervous System Disorders:	
Very common	Cerebral disorder, cerebellar disorder, somnolence
Frequency not known	Coma, convulsion, peripheral motor neuropathy, peripheral sensory neuropathy
Psychiatric Disorders:	
Frequency not known	Personality change[c]
Respiratory, Thoracic and Mediastinal Disorders:	
Very common	Acute respiratory distress syndrome, pulmonary oedema
Skin and Subcutaneous Tissue Disorders:	
Common	Skin exfoliation,

[a] With subsequent death

[b] may be prevented or diminished by prophylaxis with a local corticosteroid eyedrop

[c] Personality change was reported in association with cerebral and cerebellar dysfunction.

Peripheral motor and sensory neuropathies after consolidation with high-dose CYTOSAR, daunorubicin, and asparaginase have occurred in adult patients with acute non lymphocytic leukemia. Patients treated with high-dose CYTOSAR should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders.
Corneal toxicity consisting of ocular pain, tearing, foreign-body sensation, photophobia and blurred vision has been reported.

Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with high dose therapy than with standard CYTOSAR treatment programs.

If high dose therapy is used, do not use a diluent containing benzyl alcohol.

Intermediate dose therapy
A diffuse interstitial pneumonitis without clear cause that may have been related to Cytosar was reported in patients treated with experimental intermediate doses of CYTOSAR (1 gm/m^2) with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, VP-16).

9.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

- Definite – The AE **is clearly related** to the study treatment.
- Probable – The AE **is likely related** to the study treatment.
- Possible – The AE **may be related** to the study treatment.
- Unlikely – The AE **is doubtfully related** to the study treatment.
- Unrelated – The AE **is clearly NOT related** to the study treatment.

9.4 STRC SAE Reporting Requirements

The Safety and Toxicity Reporting Committee (STRC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix B. STRC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All WFBCCC Clinical Research Management (CRM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for STRC reporting are responsible for informing a clinical member of the STRC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

9.5 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the

prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

10.0 Pharmaceutical Information

10.1 Pharmaceutical Accountability

The drugs used in this study regimen, daunorubicin and cytarabine, are commercially available.

10.2 Daunorubicin

Product description: Anthracycline. Commercially available in 20 mg and 50 mg glass vials of red colored lyophilized drug.

Solution preparation: Each 20 mg vial is reconstituted with 4 mL of sterile water to give a final concentration of 5 mg/mL.

Storage and stability: Intact vials are stored at room temperature and protected from direct sunlight. Reconstituted solutions are stable for 48 hours when refrigerated at 2°–8°C (36°–46°F) and 24 hours at room temperature, when protected from sunlight. Do not freeze.

Route of administration: Continuous intravenous infusion over 24 hours. Compatible with cytarabine. Incompatible with sodium heparin. Vesicant.

Disposal: Care should be taken in disposing daunorubicin. Daunorubicin is a vesicant; wear proper protective equipment when handling. Dispose of per local regulations and the Wake Forest Hem/Onc Waste Disposal Guide.

10.3 Cytarabine

Product description: Antimetabolite. Commercially available in 100 mg, 500 mg, 1 gm, and 2 gm vials.

Solution preparation: For IV use, reconstitute the 100 mg vial with 5 mL bacteriostatic water for injection to achieve a concentration of 20 mg/mL. Add 10 mL of bacteriostatic water to the 500 mg vial to achieve a final concentration of 50 mg/mL. Add 10 and 20 mL of bacteriostatic water to the 1 and 2 gm vials respectively to achieve a final concentration of 100 mg/mL.

Storage and stability: The dry powder is stored at room temperature. Solutions reconstituted with sterile water without preservative should be used immediately; solutions reconstituted with Bacteriostatic of Water are stable up to 48 hours at controlled room temperature (15^{o} to 30^{o}C). Solutions with a slight haze should be discarded.

Route of administration: Continuous intravenous infusion over 24 hours.

Disposal: Care should be taken in disposing cytarabine. Dispose of per local regulations and the Wake Forest Hem/Onc Waste Disposal Guide.

12.0 Data Management

Informed consent document	ORIS
Protocol registration form	ORIS
Subject Eligibility	ORIS
Treatment response form (Appendix D)	REDCap
Cardiac function worksheet (Appendix E)	REDCap
Adverse events log (Appendix F)	ORIS

13.0 Statistical Considerations

13.1 Analysis of Primary Objective

Since this is a pilot study, several descriptive analyses will be performed. These will include examining the change in each measure of cardiotoxicity from the initial pre-chemotherapy assessment to each of the available post-chemotherapy imaging assessment (i.e. EF, LVEDV, LVESV, T1/T2 mapping, myocardial strain). These comparisons will be made using paired T-tests. Similar analyses will be performed using the ECHO-derived measures. In addition to examining the continuous changes in measures, we will determine the proportion of patients who exhibit a cardio-toxic event at 3-months defined as have a reduction in LVEF≥10% and EF≤50% when compared to baseline. This event will be defined for both the ECHO and MRI measures. In addition to point estimates of these rates, 95% confidence intervals will be calculated.

Additional toxicity measures will be tabulated after each visit.

For feasibility assessment, we will determine the proportion of patients with study-related deviations and report these proportions with 95% confidence intervals. In addition, we will determine the proportion of patients who complete the infusion therapy.

13.2 Analysis of Secondary Objective

Similar toxicity analyses as described above for the primary objective will be examined at the 6-month time point.

We will report frequencies of response status (Overall response rate [CR + CRi]; Induction death rate; Percentage of patients with persistent leukemia; Disease-free survival [for those who achieve remission]) with the number of patients in each category of response. Treatment outcomes will be stratified by age (≥60, < 60),ECOG (0-2, 3), cytogenetic risk groups and prior hematological disease (e.g. MDS, MPN).

Three sets of correlation analyses will be performed; the first will determine the correlation between ECHO and MRI assessments performed pre-chemotherapy; the second will assess correlations between post-chemotherapy ECHO and MRI assessments; and the third will assess correlations between each of the time points. In addition to the correlation analyses, paired t-tests will be performed to compare the actual values of each ECHO/MRI measurement to each other at each time point. Finally, Bland-Altman plots will be generated at baseline, follow-up and using the change in measure for each of the MRI/ECHO derived measures.

13.3 Power and Sample Size

Assuming a sample size of 32 evaluable patients (assuming a drop rate of up to 20% by 3-months) we will need to enroll 40 total patients. With n=32 patients, we have 80% power to detect a 0.511 standard deviation difference using a paired t-test assuming alpha=0.05 (2-sided). If the drop-out rate is lower (i.e., n=40) then the detectable difference would be 0.45 standard deviations. This difference should demonstrate a meaningful change in the cardiotoxic parameters of interest. In addition, with n=32 patients we can estimate the 3-month cardio-toxicity rate within +/- 0.181 using an 95% Exact Clopper-Pearson 2-sided confidence interval.

13.4 Estimated Accrual Rate

We expect to accrue at least 30 patients per year.

13.5 Estimated Study Length

Assuming a sample size of 40, we expect to accrue 30 patients per year and complete the study in <2 years.

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Appendix A – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic ☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

ECOG Performance Status: ___ ___ ___

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by ORIS): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

Appendix B – Subject Eligibility Checklist

IRB Protocol No.	WFBCCC Protocol No. 22616
Study Title: Cytarabine plus Continuous Infusion Daunorubicin Induction Therapy for Adults with Acute Myeloid Leukemia; A Feasibility Study with Cardiac MRI Monitoring	
Principal Investigator: Bayard Powell, MD	

Inclusion Criteria (as outlined in study protocol)	Criteria is met	Criteria is NOT met	Source Used to Confirm * (Please document dates and lab results)
Patients must have morphologically confirmed newly diagnosed acute myelogenous leukemia (AML) with blood or bone marrow disease. Patients with only extramedullary disease in the absence of bone marrow or blood involvement are eligible. Note: This protocol uses WHO diagnostic criteria for AML. Patients with acute promyelocytic leukemia (APL, FAB, M3) or blastic transformation of chronic myelogenous leukemia (CML) are not eligible.	☐	☐	
≥ 18 years of age.	☐	☐	
ECOG performance status 0-3.	☐	☐	
Patients with ECHO EF ≥ 45% within 28 days prior to registration.	☐	☐	
Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.	☐	☐	
Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.	☐	☐	
Ability to understand and willingness to sign an informed IRB-approved informed consent document	☐	☐	

Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Patients who have received prior induction chemotherapy for AML or MDS. Temporary prior measures such as apheresis or hydroxyurea are allowed. Patients who have received a limited and short-term exposure of ATRA (all trans retinoic acid) while AML-M3 (Acute Promyelocytic Leukemia) was being ruled out, and which has been discontinued, will be eligible.	☐	☐	
Patients receiving any other investigational agents.	☐	☐	
Patients with prolonged QTc interval (> 500 msec) determined by EKG within 28 days prior to registration.	☐	☐	
Patients not suitable for cardiac MRI. Contraindications include: • Intracranial metal, pacemakers, defibrillators, functioning neurostimulator devices, or other implanted electronic devices; • Ferromagnetic cerebral aneurysm clips, or other intraorbital/intracranial metal; • Allergy to Gadolinium or other severe drug allergies; • Claustrophobia; • Congestive heart failure (NYHA class III or IV); • Significant valvular disease, or significant pulmonary disease requiring supplemental oxygen therapy	☐	☐	
History of allergic reactions attributed to compounds of similar chemical or biologic composition to daunorubicin or cytarabine.	☐	☐	
Patients with documented CNS involvement.	☐	☐	
Patients who are known to be HIV+ may be eligible providing they meet all of the following additional criteria within 28 days prior to registration: • CD4 cells ≥ 500/mm3 • Viral load of < 50 copies HIV mRNA/mm3 if on cART or < 25,000 copies HIV mRNA if not on cART • No zidovudine or stavudine as part of cART Patients who are HIV+ and do not meet all of these criteria are not eligible for this study.	☐	☐	
Patients with other uncontrolled intercurrent illness or psychiatric illness/social situations that would limit compliance with study requirements.	☐	☐	

Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects with drugs used in this study. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with the drugs used in this study, breastfeeding should be discontinued prior to beginning treatment.	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

ORIS Assigned PID: _____

Signature of research professional confirming eligibility:_____ Date: _____

Signature of Treating Physician**: _____ Date: _____

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”
**Principal Investigator signature can be obtained following registration if needed

Appendix C – Mandatory STRC SAE Reporting Guidelines

Safety and Toxicity Review Committee (STRC; previously known as CROC) Serious Adverse Event (SAE) Notification SOP	**Date: 11/17/2016**

Mandatory STRC SAE Reporting Requirements

This document describes STRC reporting and use of the electronic submission form that is submitted **for unexpected grade 4 and any grade 5 (death during protocol intervention) SAEs on CCCWFU Institutional interventional trial patients**. There are multiple entities that require reporting of SAEs. Each entity has different rules for what is reported, and how it is reported.

Rules used by other entities (Institutional Review Board (IRB), AdEERS, MedWatch, etc.) should NOT be used to evaluate whether an event should be reported to STRC. Only the rules for reporting described in this document should be considered.

As defined in the NCI Data Table 4 reporting guidelines, **CCCWFU Institutional Interventional studies covered by these reporting requirements are defined as: In-house, internally reviewed trials, including those collaborative studies conducted with industry sponsorship in which the center is a primary contributor to the design, implementation, and monitoring of the trial, or participation in a multi-site trial initiated by an institutional investigator at another center.** Institutional trials are almost always authored by a researcher here at CCCWFU. Institutional protocols are labeled NCI Code="I" for Institutional on the protocol screen in ORIS. Cooperative group protocols are **not** considered Institutional, but Research Base trials **are** classified as Institutional.

The STRC is responsible for reviewing SAEs for CCCWFU Institutional Interventional studies, as defined above. STRC currently requires that unexpected grade 4 and all grade 5 SAEs on these trials be reported to the STRC for review. All Clinical Protocol and Data Management (CPDM) staff members assisting a PI in documenting and reporting an SAE that qualifies for STRC reporting are responsible for informing a clinical member of the STRC by phone (or in-person), followed by informing the entire committee via the required email notification.

THESE REPORTING REQUIREMENTS APPLY TO any faculty or staff member on the study team for a CCCWFU Institutional Interventional trial. Once an event is observed, it is the responsibility of the person who observed the event to be sure that it is reported.

What is considered an SAE under this mandatory procedure?
Any **unexpected grade 4** event and **all grade 5 events** (death during protocol intervention) should be reported. These events should be reported if they occur while a patient is on study treatment or if they occur within 30 days of last study treatment (even if patient begins a new treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. In addition, if it is not clear whether the Grade 4 is unexpected it should be reported.

Table 1: Summary of STRC Reporting Requirements for Institutional Pilot, Phase 1, Phase 2 and Phase 3 Interventional Trials

STRC reporting may not be appropriate for specific expected adverse events for protocols. In those situations the adverse events that will not require STRC reporting **must be specified in the text of the approved protocol.**

	ADVERSE EVENT					
	Grade 1, Grade 2, Grade 3		Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected
Unrelated	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Unlikely	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Possible	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Probable	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Definite	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**

STRC notification responsibilities of the person handling the reporting/documenting of the SAE:

1. Make a phone call (or speak in person) to the appropriate clinical member of the STRC as listed below (page if necessary)—see note 2 below
2. Submit the STRC Notification Form WITHIN 24 HOURS of first knowledge of the event. This form is found at either the ORIS main menu page or by going to http://ccc.wfubmc.edu/oris/strc.aspx. This will ensure that all persons that need to be made aware of the event (i.e., study team members and STRC members) will be notified; remember to file a copy of your confirmation. (Form instructions will walk you through the required fields, consult the help page for further instructions.)
3. Ensure that you document that the appropriate person(s) on the STRC has been contacted. This documentation is placed on the STRC Notification form described above.
4. Follow up with/update the clinical member(s) of STRC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements to complete the electronic STRC form:
Please use 'reply to All' when responding with one of these terms: Definite, Probable, Possible, Unlikely, or Unrelated

1. Patient ID (ORIS PID)
2. Patient Name
3. Patient MR#

4. CCCWFU(ORIS) Study Number
5. Title
6. PI Name
7. PI Contact Number
8. PI Comments
9. STRC Clinician notified by Phone
10. Notified Date
11. Notified Time
12. STRC Clinician Comments
13. Category [This is the Grade – Either Unexpected Grade 4 or Grade 5 should be entered]
14. Additional Information (IRB Reporting)(after discussion with PI or STRC Clinician
    i. Is This Event Related to Protocol Treatment?
    ii. Is Suspension of the Protocol Needed?
    iii. Any Changes to Consent or Protocol Needed?
    iv. Was Nature or Severity of Event Unexpected?
15. Date of the event.
16. Brief description (include brief clinical history relevant to this event, including therapies believed related to event).
17. Date of Last Dose before event
18. Relevant tests/labs.
19. Other Relevant Treatment Information
20. Other Comments/Notes (include regimen of chemo and dates the patient received them if known).
21. Cc (email) (include treating Physician; separate email list with comma”,”)
22. Your Name
23. Your Email
24. Confirm Your Email

The Clinical Members of STRC to Notify by Phone or Page:

Bayard Powell, MD – Director-at-Large, CCCWFU; Section Head, Hematology/Oncology
Glenn Lesser, MD – Hematology Oncology
Stefan Grant, MD, JD-Hematology Oncology
Jimmy Ruiz, MD-Hematology Oncology
Kathryn Greven, MD – Vice Chair – Radiation Oncology
Marissa Howard-McNatt, MD – General Surgery
Mercedes Porosnicu, MD- Hematology Oncology

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within a reasonable amount of time, then initiate contact with their backup. Give the back-up a reasonable amount of time to respond to a phone call or page before contacting another member. This is a general guideline. You must use your best judgment as a clinical research professional given the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate

and proceed with submitting your STRC notification form. The important criteria is that you have taken reasonable steps to notify and document that you have initiated some type of contact to one or more of the clinical members of STRC.

STRC CLINICAN RESPONSIBILITY:

It is the responsibility of the STRC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of STRC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. STRC reserves the right to agree with the investigator's assessment if STRC does not agree with the investigator. STRC reserves the right to suspend the trial pending further investigation.

Is there any immediate danger or harm that could be present for a future patient based on the information provided in the STRC report – and if so an immediate suspension of enrollment should take place.

AMENDMENTS TO PREVIOUS REPORTS

If you are not able to supply all pertinent information with the initial submission, once the additional information is available **do not submit a new report**. Go to the original email that was received by STRC and others "reply to all" and entitle your email "**Amendment** for (list date of event and patient ID) this will avoid duplications of the same event. List the additional information which you are reporting.

Acronyms and Definitions

STRC-Safety and Toxicity Review Committee
SAE-Serious Adverse Event
IRB-Institutional Review Board
CCCWFU-Comprehensive Cancer Center Wake Forest University
ORIS-Oncology Research Information System
NCI-National Cancer Institute
CPDM-Clinical Protocol and Data Management
Interventional Trials-Therapeutic Level 1 and Level 2 trials
Therapeutic Level 1-A cancer treatment protocol aimed at directly treating/curing the patient's cancer.
Therapeutic Level 2-A therapeutic protocol not cancer treatment involves clinical activity to treat symptoms, improve the patient's quality of life, or preven

Appendix D - Response Criteria[14]

Date: ___ ___ / ___ ___ / ___ ___

Allogeneic stem cell transplant received? ☐ Yes ☐ No Date: __ __/__ __/__ __

Please check the response that applies to this patient:

☐ Morphologic leukemia-free state
☐ Complete Remission (CR)
☐ Complete Remission with Incomplete Recovery (CRi)
☐ Cytogenetic Complete Response (CRc)
☐ Molecular Complete Response (CRm)
☐ Partial Remission (PR)

Treatment Failures
☐ Treatment Failure due to Resistant Disease (TFRD)
☐ Treatment Failure due to Complication of Aplasia (TFCA)
☐ Treatment Failure due to Indeterminate Cause (TFIC)
☐ Morphologic Relapse
☐ Molecular or cytogenetic relapse
☐ Induction Death

Treating Physician Signature: _____ Date: ___ ___ / ___ ___ / ___ ___

PI Signature: _____ Date: ___ ___ / ___ ___ / ___ ___

Appendix E: Cardiac Function Worksheet

Cardiac Function Worksheet					
PID_____ Study Number_____ MRN_____ Continuous infusion completed? Y / N[#] [#]If No, Amount infused: _____ml Duration: _____hrs _____min		Baseline (Pre-Induction) Date: ___/___/___	*Prior to Induction Cycle 2 Date: ___/___/___	3 mo. follow-up or relapse 3 Mo.___ Follow-up___ Date: ___/___/___	6 mo. follow-up or relapse 6 Mo.___ Follow-up___ Date: ___/___/___
MRI		w/o contrast	NA	w/o contrast	w/o contrast
EF	%				
LVEDV	ml				
LVESV	ml				
Mean T1					
Mean T2					
Global longitudinal strain	%				
MRI Completed		Y / N	NA	Y / N	Y / N
Person recording information					
ECHO		Full 3D	Ltd w/ strain	Ltd w/ strain	NA
EF	%				
LVEDV	ml				
LVESV	ml				
Global longitudinal strain	%				
ESV	ml				
Mitral inflow E velocity					
Mitral inflow A velocity					
Mitral inflow A' velocity					
Mitral inflow E' velocity					
ECHO Completed		Y / N	Y / N	Y / N	NA
Person recording information					
Troponin Levels					
		Pre-Induction	Cycle 1/ Day 4	*Cycle 2/ Day 3	Notes
Levels		ng/ml	ng/ml	ng/ml	
Brand of troponin assay used#					
Person recording information					
# 1 = TnI-Ultra Assay, Siemens (Centaur) 2 = Access 2 AccuTnI+3 Assay Beckman Coulter					
Definitions					
MRI = Magnetic Resonance Imaging			ESV = End systolic volume		
ECHO = Echocardiogram			ml = milliliters		
EF = Ejection Fraction			LVESV = left ventricular end systolic volume		

LVEDV = left ventricular end diastolic volume	* only for those requiring a second cycle of induction
Ltd w/ strain = Limited with strain measures	w/o contrast = without contrast

INSTRUCTIONS FOR COMPLETING THE CARDIAC FUNCTION WORKSHEET

Purpose: This purpose of this form is to record data related to cardiac function as derived from the two of the main study tasks; magnetic resonance imaging (MRI) and echocardiogram (ECHO).

1. Record the patient information in the appropriate spaces (name, study number, MRN).
2. Transfer data regarding infusion completion.
3. At each time point, fill in the date.
4. Before performing each task note the specification for the procedure within each time point (grayed row).
5. Record the data for each task.
6. At the end of the data collection for each task (MRI or ECHO), circle “Y” or “N” to indicate whether the patient was able to complete the study task.
7. For the individual recording the data, please sign or initial at the bottom of the data collection form in the “Person recording information” line in either the MRI or ECHO section .
8. For the troponin levels, enter the brand of assay being used with either a 1 or 2 using the key designated by #
    a. Enter the levels once obtained in ng/ml
9. Those entering data please sign the designated section “person recording information” in the Troponin levels section

Appendix F – Adverse Event Log

WFBCCC Adverse Event (AE) Log

PI: _____ PID: _____ MRN: _____

Cycle Start Date: _____ Cycle End Date: _____ Cycle #: _____

Adverse Event CTC Term	**Value** (-5 if non-numeric)	**Grade** (0-5) per CTC	**Start Date**	**Attribution** 1=Related 2=Probably 3=Possible 4=Unlikely 5=Unrelated	**Treating MD Initials/Date**	**End Date**	**Expected** 1=Yes 0=No	***Serious Adverse Event (SAE)** 1=Yes 0=No	**Dose Limiting Toxicity (DLT)** 1=Yes 0=No	**Action Taken** 1=None 2=Tx withheld 3=Tx D/C 4=Tx adjusted 5=Other	**Reportable?** 1=IRB 2=STRC 3=FDA 4=Sponsor

*Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

CTCAE Version 4- http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE 4.03 2010-06-14 QuickReference 8.5x11.pdf