Comprehensive Cancer Center of Wake Forest University

CCCWFU #99113 – Investigating the Prognostic Importance of Bioelectrical Impedance Phase Angle in Adults Treated for Newly Diagnosed Acute Leukemia

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NCT01869777

Protocol Version Date 07.25.14

1.0 Background and Rationale

The acute leukemias in adults are characterized by resistance and poor outcomes. Acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) are aggressive malignancies that lead to the accumulation of immature myeloid or lymphoid precursors, resulting in progressive marrow failure and death [1]. They affect approximately 19,000 people per year in the United States; despite decades of research, the overall 5-year survival remains a disappointing 30-40% [2-4]. The current treatment is intensive induction chemotherapy followed by consolidation using chemotherapy or a stem cell transplant [2,5].

Selecting patients for intensive therapy is a major challenge in the acute leukemias. There are multiple prognostic factors in the acute leukemias that are used to try and select the best candidates for intensive induction therapy. The most powerful single prognostic factor in the acute leukemias is cytogenetics. Using standard karyotyping techniques patients can be divided into 3 prognostic categories; good, intermediate and poor. They are characterized by 5 year overall survival rates of 55%, 24% and 5% respectively [6]. Age is also a powerful prognostic factor in the acute leukemias. For patients over 60 with acute leukemia, the prognosis is grave (five-year survival of less than 10%) [7-9]. These patients have many co-morbidities and increased resistant disease [2,5]. Both acute leukemias in adulthood disproportionately affect the elderly (median age of onset of 72 and >60 for AML and ALL, respectively) [4,10]. The presence of poor-risk cytogenetic factors is increased in elderly patients as well as expression of multi-drug efflux pumps [11-12]. Performance status is another important prognostic factor and the ability to tolerate induction therapy decreases as performance status worsens regardless of age [8]. For older patients with poor performance status it is currently acceptable clinical practice to offer only supportive care. In AML this has led some authors to conclude that standard induction chemotherapy should not be offered to elderly patients[13]. In contrast other groups have found a positive clinical impact of standard therapy in older AML patients with increased survival and less time in hospital than those offered only supportive care[14]. In order to better help clinicians decide what patients should be offered intensive therapy a number of prognostic scoring systems have been developed[15]. The majority of these systems rely heavily on the cytogenetics of the leukemia and this information is generally not available at the time of diagnosis. An additional prognostic factor that could be easily obtained at the time of diagnosis would a major step forward. In addition to deciding on what initial therapy to give an AML patient there is another major clinical decision point. A nadir marrow is obtained on day 14 following standard induction therapy and if there is significant residual disease a second course of induction is usually attempted. In many cases patients have experienced significant complications by day 14 making additional chemotherapy difficult to safely administer. There are very few studies on what prognostic factors are important when considering a second course of induction therapy. This is further complicated by the lack of rigorously performed studies to establish the predictive power of a positive nadir marrow. An additional prognostic factor that could be easily obtained on day 14 would be of significant help to clinicians.

Bioimpedance phase angle is prognostic in multiple disease states. Phase angle is measured by bioimpedance and reflects cell membrane integrity, nutritional status and muscle mass[16]. It has been found to be prognostic in a number of conditions such as end stage renal disease, HIV and COPD[17-19]. Additionally, it is prognostic in multiple tumor types including pancreatic, colorectal, breast and head and neck. In a recent report it was found to be strongly prognostic for patients with hematologic malignancies undergoing allogeneic stem cell transplants[20]. Standardized phase angle measurements are made non-invasively, can be done quickly and reproducibly and with no patient discomfort. Measurements are taken by placing 2

electrodes on the hand and 2 on the foot from the same side of the patient. A small voltage is applied between the electrodes and the timing of induced the current is measured. The current is approximately 1000 times lower than the sensitivity of sensory neurons and thus cannot be felt by the patient and has no known biological effect. This study seeks to establish the feasibility and prognostic power of standardized phase angle in acute leukemia patients undergoing intensive induction chemotherapy.

2.0 Objectives

2.1 To determine the feasibility of obtaining standardized phase angle measurements on patients hospitalized for treatment of newly diagnosed acute leukemia.

2.2 To evaluate the association between standardized phase angle measured at the start of therapy and treatment-related outcomes including:
Primary outcome: Treatment related mortality (defined as 60-day mortality)
Secondary outcomes: Evaluate the association of the day 14 standardized phase angle and treatment related outcomes, 30-day mortality, length of hospitalization, transfer to intensive care unit during induction, treatment response (14 day bone marrow response, complete remission), receipt of post-remission therapy, overall survival.

2.3 An exploratory analysis investigating associations with the primary and secondary outcomes using different ways to categorize the baseline standardized phase angle measurement (obtained on the first day of treatment) and, for AML patients, the standardized phase angle measure obtained just prior to the nadir marrow.

3.0 Patient Selection Criteria

3.1 Eligible

- 3.11 Hospitalized for newly diagnosed acute leukemia
- 3.12 Receiving induction treatment while hospitalized
- 3.13 Willing and able to provide written informed consent

3.2 Ineligible

- 3.21 Presence of a pacemaker or defibrillator.
- 3.22 Patients pregnant at the time of enrollment.
- 3.23 Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients.
- 3.24 Unable/unwilling to follow protocol requirements

4.0 Study Design

Eligible patients with newly diagnosed acute leukemia will have phase angle measurements recorded within the first 3 days of treatment. AML patients will have a second phase angle measurement taken within 2 days of the nadir marrow. Whenever possible, measurements will be taken prior to any invasive procedures (bone marrow biopsy, leukophoresis, PICC line placement, etc.). In addition data on pertinent covariates including age, demographic data, tumor biology, white blood cell count, LDH, need of total parental nutrition or placement of a feeding tube and comorbid conditions

will be collected. There will be no intervention done as a result of the phase angle measurement. Patients will be followed at routine visits per standard of care for two years or until death.

5.0 Data Management

All data will be de-identified and stored in a password protected REDCap database in accordance with HIPAA. Research Electronic Data Capture (REDCap) software is a secure, web-based application designed to support survey creation, survey administration and data capture for research studies. Records to be kept on each subject will include only the data specified in Appendices B, C, D, E and F. Only study personnel will have access to the data.

6.0 Registration

Eligible patients must be registered with the CCCWFU Registrar. Following registration, patients should have a baseline phase angle measurement taken. If a patient does not agree to have the measurement following registration, the patient's registration on the study may be canceled. The Registrar should be notified of cancellations as soon as possible.

To register a patient, the following documents should be completed by the research nurse or data manager and faxed (336-713-6772) to the Registrar:

- Signed patient consent form/HIPAA authorization form
- On-Study/Registration Form (Appendix A)

The research nurse or data manager will then call (336-713-6767) the Registrar between the hours of 0800-1600 EST Monday-Friday to verify eligibility. To complete the registration process, the Registrar will:

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

7.0 Statistical Considerations

Description of measures

Standardized phase angle

Standardized phase angle will be calculated as in [20] (standardized phase angle = (measured phase angle−phase angle ref)/SD ref). Reference values and standard deviation come from measurements of phase angle in over 200,000 healthy German adults[21].

Mortality

30 day mortality rate is defined as the percent of patients no longer alive at 30 days after registration. In the rare case that a patient is lost to follow up before 30 days, the patient will be treated as missing.

60 day mortality rate is defined as the percent of patients no longer alive at 60 days after registration. Patients that are discharged to hospice care before 60 days without a known date of death will be counted towards 60 day mortality. In the rare case that a patient is lost to follow up before 60 days, the patient will be treated as missing.

Treatment response
14 day bone marrow response is defined as hypoplastic marrow with less than 20% cellularity and 5% blasts.

Complete remission is defined as less than 5% marrow blasts, absolute neutrophil count >1000, platelet count >100,000 and freedom from red cell transfusions.

Feasibility Analysis
If the study fails to accrue 20 patients during the first year of accrual it will be deemed unlikely to meet its ultimate accrual goal and the study will be terminated.

Primary analysis
This study's primary endpoint is the association between standardized phase angle and 60 day mortality. Standardized phase angle will be treated as a continuous measure for the primary analysis. Since we will be using a standardized measure of phase angle, for power calculations we will assume a standard deviation of one and investigate the effects of a one unit change. A sample size of 102 patients would give us 80% power to detect an odds ratio of 2.1, using a logistic regression model with a 0.05 significance level and a 60 day mortality rate of 20%. With an expected accrual rate of 50 patients per year, the study should complete accrual in approximately two years and complete follow-up (two year follow-up) four years after the first patient is enrolled. Descriptive statistics will be used for baseline characteristics. Important baseline characteristics, such as age, will be added to the regression model as covariates for additional analysis.

Secondary analysis
We will use logistic regression to analyze the association between standardized phase angle and the secondary outcomes of 30 day mortality, transfer to the intensive care unit, 14 day marrow response, complete remission and receipt of post-remission therapy. The association with overall survival will be evaluated using a Cox proportional hazards model. We will use a linear model to look at the association with length of hospital stay. It is likely that the length of hospital stay will not be normally distributed and will need a transformation to satisfy the normality assumption of the linear model. Feasibility will be analyzed qualitatively.

Exploratory analysis
We will explore other versions of the standardized phase angle measure and how they relate to the primary and secondary outcomes. We will evaluate using categorical cut points of the baseline measure and the standardized phase angle measure captured just prior to the nadir marrow (for AML patients).

8.0 Protection of Human Subjects
Prior to implementation of this study, the protocol will be approved by the WFU Institutional Review Board (IRB). All subjects will provide written informed consent prior to enrollment in the study.

9.0 Data Submission Schedule

Appendix A – Eligibility Checklist and Registration Form:
- Submitted to Registrar at the time of registration

Appendix B – Demographics, Social and Medical History, Baseline Lab Data Collection Form:
- completed at study entry

Appendix C – Comorbidity Data Collection Forms:
- completed at the time of initial phase angle measurement
-submitted within one week of completion

Appendix D – Phase Angle Measurement Form:
- completed each time a phase angle measurement is made (i.e. 1st day of treatment, prior to nadir marrow [AML patients only], and prior to any invasive procedures)
-submitted within one week of completion

Appendix E – Bone Marrow Biopsy and Treatment Data Collection Form:
-completed as appropriate
-submitted within one week of completion

Appendix F – Follow-up Data Collection Form
- completed as appropriate
-submitted within one week of completion

10.0 References

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Appendix A - Eligibility and Source Document Checklists, Registration Form

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REGISTRATION GUIDELINES

The following guidelines have been developed in order to ensure timely registration of your patient.

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

In order to ensure prompt registration of your patient, please:

1. Complete the Eligibility Checklist (attached)
2. Complete the Protocol Registration Form (attached)
3. Alert the WFUHS 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. Please 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, please provide a printout of the results. Please ensure that the most recent lab values are sent.

CCCWFU # 99113 **Eligibility Checklist** **Page 1**

Yes	No	N/A	Inclusion Criteria (All responses must be **YES** in order to enter study)	Eligibility Confirmation (registrar)
☐	☐	☐	1. Is the patient hospitalized for newly diagnosed acute leukemia?	
☐	☐	☐	2. Is the patient receiving induction treatment while hospitalized?	
☐	☐	☐	3. Is the patient willing and able to provide written informed consent?	
Yes	**No**	**N/A**	Exclusion Criteria (All responses must be **NO** in order to enter study)	
☐	☐	☐	1. Does the patient have a pacemaker or defibrillator?	
☐	☐	☐	2. Is the patient pregnant?	
☐	☐	☐	3. Does the patient have any abnormality which may, in the opinion of the investigator, compromise the safety of patients?	
☐	☐	☐	4. Is the patient unable or unwilling to follow protocol requirements?	

Signature: _____ Date: _____
Please send source documentation with Eligibility 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)

Zip Code: ___ ___ ___ ___ ___

Primary Diagnosis: _____

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

PROTOCOL INFORMATION

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

MD Name (last) : _____

Informed written consent (consent must be signed prior to registration):

☐ YES ☐ NO

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.

CCCWFU # 99113 Eligibility Source Documentation Checklist Page 3
(to be submitted with Protocol Registration Form)

Source Documents Needed		✓ or N/A
1	Documentation that patient is hospitalized for newly diagnosed acute leukemia	
2	Documentation that patient is receiving induction treatment while hospitalized	
3	Signed informed consent document	
4	Documentation that patient is not pregnant	
5	Documentation that patient is free from any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients	

Appendix B: Social and Medical History, Baseline Lab Data Collection Form (Page 1 of 2)

Demographics
Social History:

Married: Yes ___ No ___

Tobacco use: Current _____ Former _____ Never _____

Alcohol abuse: Current _____ Former_____ Never _____

Baseline Labs on date of admission: (allow one decimal point)

WBC	___ ___.___	SODIUM	___ ___.___
HEMOGLOBIN	___ ___.___	POTASSIUM	___ ___.___
HEMATOCRIT	___ ___.___	BUN	___ ___.___
		GLUCOSE	___ ___.___
PLATELETS	___ ___ ___	CREATININE	___ ___.___
NEUTROPHILS	___ ___.___	ALBUMIN	___ ___ ___
BANDs	___ ___.___	T. BILIRUBIN	___ ___.___
ANC	___ ___.___	ALK PHOS	__ ___.____
		AST	___ ___.___
LDH	___ ___.___	ALT	___ ___.___
		GFR	___ ___.___

Appendix B: Demographics, Social and Medical History, Baseline Lab Data Collection Form (Page 2 of 2)

Past Medical History

Number of comorbidities: _____ (0-20)

Past History of:
(per documentation in medical record at time of admission)

Congestive Heart Failure	Y___ N___	Depression	Y___ N___
Coronary artery disease	Y___ N___	Osteoporosis	Y___ N___
Cerebrovascular Disease (Stroke, TIA)	Y___ N___	Rheumatologic disease (SLE, RA, scleroderma, Sjogrens)	Y___ N___
Diabetes Mellitus	Y___ N___	Cognitive Impairment	Y___ N___
COPD (Emphysema)	Y___ N___	VTE (Venous thrombosis, DVT, PE)	Y___N___
Hypertension	Y___ N___	Cardiac valve disease	Y___ N___
Renal Dysfunction	Y___ N___	Cirrhosis	Y___ N___
Previous Cancer (Excludes non-melanoma skin)	Y___ N___	MDS (H&P only)	Y___N___
		MDS (path report only)	Y___N___

If yes, then cancer type _____

Prior treatment with: (check) Chemotherapy ___ Radiation ___ Surgery ___

Appendix C: Comorbidity Data Collection Forms (Page 1 of 3)

Charlson Comorbidity Index

Comorbidity and score (circle)

Myocardial infarction	1
Congestive heart failure	1
Cerebrovascular disease	1
Peptic ulcer	1
Hepatic ulcer (mild)	1
Diabetes (mild/moderate)	1
Pulmonary disease (mild/moderate)	1
Diabetes (with severe end stage organ damage)	2
Renal disease (moderate or severe)	2
Hepatic disease (moderate or severe)	3
Solid tumor with metastases	6

Total Score_____

Appendix C: Comorbidity Data Collection Forms (Page 2 of 3)

Hematopoietic Cell Transplant Comorbidity Index (HCT-CI)

Comorbidity and score (circle)	
Cardiac (CAD, CHF, MI, EF ≤ 50%)	1
Arrhythmia (Atrial fibrillation or flutter, sick sinus or ventricular arrhythmia)	1
Cerebrovascular disease (TIA or CVA)	1
Peptic ulcer (Requiring treatment)	2
Hepatic Disease (mild) (Chronic hepatitis, bilirubin>ULN to 1.5 X the ULN,or AST/ALT>ULN to 2.5 X the ULN)	1
Diabetes (Requiring treatment with medication)	1
Pulmonary (moderate) (DLCO and/or FEVI 66-80% or dyspnea with slight activity)	2
Rheumatologic (SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica)	2
Inflammatory bowel disease (Crohns disease or ulcerative colitis)	1
Renal (moderate/severe) (Serum creatinine>2mg/dL, mixed CTD, or prior renal transplant)	2
Prior solid tumor (Treated at any point in patient's history, excluding non-melanoma)	3

Appendix C: Comorbidity Data Collection Forms (Page 3 of 3)

Hepatic (moderate/severe) (Liver cirrhosis, bilirubin>1.5 X the ULN, or AST/ALT>2.5 X the ULN)	3
Obesity (Body mass index > 35 kg/m²)	1
Infection (Requiring use of antimicrobial treatment)	1
Psychiatric Disturbance (Depression or anxiety requiring psychiatric consult or treatment)	1
Heart Valve Disease (Except mitral valve prolapse)	3
Severe pulmonary (DLCO and or FEVI ≤ 65% or dyspnea at rest or requiring oxygen)	3

Total score: _____

Appendix D – Phase Angle Measurement Form

To be completed with each phase angle measurement:

ORIS Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

Physical Exam:

Date of Exam: ___ ___ / ___ ___ / ___ ___

Weight: ____ (kg)

Height: _____ (cm)

Systolic Blood Pressure (SBP): _____ (50-250)

Diastolic Blood Pressure (DBP): _____ (30-130)

Pulse: _____ (30-180)

Phase Angle: _____ R:_____ Xc_____

For AML Patients: Second Phase Angle Measurement taken just prior to the nadir marrow:

Physical Exam:

Date of Exam: ___ ___ / ___ ___ / ___ ___

Weight: ____ (kg)

Height: _____ (cm)

Systolic Blood Pressure (SBP): _____ (50-250)

Diastolic Blood Pressure (DBP): _____ (30-130)

Pulse: _____ (30-180)

Phase Angle: _____ R:_____ Xc_____

Appendix E – Bone Marrow Biopsy and Treatment Data Collection Forms

BONE MARROW BIOPSY:

DATE _____/_____/_____

Diagnosis: AML or ALL _____ Blast %: _____

CYTOGENETICS: _____(free text)

RISK GROUP: FAVORABLE ___ INTERMEDIATE ___ UNFAVORABLE ____

APL: YES___ NO___ Hypoplastic marrow cellularity %: _____

TREATMENT:

HOSPITALIZED FOR INDUCTION CHEMOTHERAPY: Y___ N___

DATE OF ADMISSION: _____

DATE OF DISCHARGE: _____

DATE INDUCTION CHEMOTHERAPY INITIATED: _____

TYPE OF CHEMOTHERAPY ADMINISTERED (*check one*):

1. ___ AraC+anthracycline+etoposide (7+3+3)
2. ___ AraC+ anthracycline (7+3)
3. ___As per CALGB 10102
4. ___other _____*(document regimen)*

NUMBER OF CYCLES OF CHEMOTHERAPY: _____(*range 0-5*)

RESIDUAL DISEASE ON 14-DAY BONE MARROW BIOPSY: Y___ N____ N/A____

REQUIRED ICU DURING HOSPITAL STAY: Y___ N___

DEATH WITHIN 30 DAYS OF INITIAL TREATMENT: Y ___ N___

DEATH WITHIN 60 DAYS OF INITIAL TREATMENT: Y ___ N___

DISPOSITION: HOME ____ SNF ____ALF ____ HOSPICE ___ DECEASED ____

Need for total parenteral nutrition or feeding tube placement during induction hospitalization:

Y____ N____

Appendix F -FOLLOW-UP (POST INDUCTION HOSPITALIZATION) Data Collection Form (page 1 of 2)

ACHIEVED COMPLETE REMISSION: Y____ N____
Comment for Complete Remission: _____(free text, 200 characters)
RECEIVED POST-REMISSION THERAPY: Y____ N____
Number of cycles of consolidation therapy: _____ (0-5)

Complete consolidation information below as applicable:

Date of 1st consolidation: _____

Specify type of 1st consolidation: hypomethylating agent (5-azacitidine/decitabine) ___

autologous transplantation___

reduced intensity allogeneic transplant___

full allogeneic transplant ___

Ara-C ____

If received Ara-C for 1st consolidation, record dose:
3gm/m^2__ 2 gm/m^2__1.5 g/m^2__1gm/m^2__ 500mg/m^2___

Other___

If other record type: _____
(text, 50 characters)

Date of 2nd consolidation: _____

Specify type of 2nd consolidation: hypomethylating agent (decitabine/azacitidine) ___

autologous transplantation___

reduced intensity allogeneic transplant___

full allogeneic transplant ___

Ara-C ____

If received Ara-C for 2nd consolidation, record dose:
3gm/m^2__ 2 gm/m^2__1.5 g/m^2__1gm/m^2__ 500mg/m^2___

Other___

If other record type: _____
(text, 50 characters)

Appendix F -FOLLOW-UP (POST INDUCTION HOSPITALIZATION) Data Collection Form (page 2 of 2)

Date of 3rd consolidation: _____

Specify type of 3rd consolidation: hypomethylating agent (decitabine/azacitidine) ___

autologous transplantation___

reduced intensity allogeneic transplant___

full allogeneic transplant ___

Ara-C ____

If received Ara-C for 3rd consolidation, record dose:
3gm/m^2__ 2 gm/m^2__1.5 g/m^2__1gm/m^2__ 500mg/m^2___

Other___

If other record type: _____
(text, 50 characters)

RECEIVED BONE MARROW TRANSPLANTATION: Y____ N____

IF YES, SPECIFY TYPE: (PICK ONE) REDUCED INTENSITY ____
FULL ALLOGENEIC ____
AUTOLOGOUS ____

SPECIFY REGIMEN: _____ (FREE TEXT, 100 characters)

Date of bone marrow transplant: _____

Appendix G – Survival Data

ORIS Assigned PID:____ ___ ___ ___ ___ ___ ___ ___

Visit Date: ____ / ____ / _____

Visit Interval:

_____ 3 Mos Post **_____** 6 Mos Post _____ 9 Mos Post _____ 12 Mos Post

_____ 15 Mos Post _____ 18 Mos Post _____ 21 Mos Post _____ 24 Mos Post

_____ Other Mos Post _____ Number of Months Post Discharge

DATE OF LAST CONTACT: ____ / ____ / _____

DECEASED: Y____ N____

DATE OF DEATH: ____ / ____ / _____