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Protocol Page

Phase I/II Randomized Study of Clofarabine, Idarubicin, and Cytarabine (CIA) versus Fludarabine, Idarubicin, and Cytarabine (FLAI) in Acute Myelogenous Leukemia and High-Risk Myelodysplastic Syndrome

2010-0788

Core Protocol Information

Short Title	Clofarabine, Idarubicin, and Cytarabine (CIA) versus Fludarabine, Idarubicin, and Cytarabine (FLAI) in AML and High-Risk Myelodysplastic Syndrome
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Full Title:	Phase I/II Randomized Study of Clofarabine, Idarubicin, and Cytarabine (CIA) versus Fludarabine, Idarubicin, and Cytarabine (FLAI) in Acute Myelogenous Leukemia and High-Risk Myelodysplastic Syndrome
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Which Committee will review this protocol?

◉ The Clinical Research Committee - (CRC)

Protocol Body

2010-0788 - Phase II Randomized Study of CIA vs FLAI - Oct 10 2013.doc

Phase I/II Randomized Study of Clofarabine, Idarubicin, and Cytarabine (CIA) versus Fludarabine, Idarubicin, and Cytarabine (FLAI) in Acute Myelogenous Leukemia and High-Risk Myelodysplastic Syndrome

I. OBJECTIVES

Phase I

Primary:

Determine the MTD of clofarabine to be used in portion II of the study.

Phase II

Primary:

Compare the response rates of two different regimens CIA versus FLAI

Secondary:

Evaluate the durability of response, the overall and event-free survival rates, and the safety profile of 2 different regimens.

II. RATIONALE

Treatment options for relapsed and refractory AML and high-risk MDS are limited. Retreatment with a high-dose cytarabine (HDAC) containing regimen is considered standard for patients relapsing after an initial complete remission (CR) lasting for a year or more. Once a second remission is achieved, these patients can proceed to stem cell transplant if appropriate donors are available. For patients relapsing after a shorter

remission or with primary refractory disease no true standard options exist and investigational therapy is considered appropriate.

We have been using fludarabine and ara-C (FA) combination chemotherapy since 1989 for relapsed AML, and since 1991 for newly diagnosed AML/MDS. We have reported that FA is superior to ara-C in relapsed AML, if disease is sensitive to ara-C as manifested by a relatively long first remission. [1] In patients with newly diagnosed disease, the use of FA- containing regimens was associated with higher complete response rates (50-60%) than with standard chemotherapy.[2] The effectiveness of FA is believed due to the ability of fludarabine to modulate the pharmacologic behavior of ara-C. Specifically, at intracellular concentrations of $\geq 10 \mu$ M, F-ara-ATP, the active metabolite of fludarabine, increases accumulation of ara-CTP in AML cells beyond that possible with dose escalation of ara-C.[3] Once above 10 μ M F-ara-ATP, ara-CTP formation plateaus.

Single agent clofarabine has demonstrated activity in phase I studies in AML.[4] As a potent inhibitor of ribonucleotide reductase (RNR) and by means of biochemical modulation, clofarabine is more ideally suited to be incorporated into combinations such as have been tested and validated with fludarabine and cytarabine in AML in the past.[5] We have previously conducted a study combining cytarabine with clofarabine in patients with relapsed/refractory AML.[6] At doses of 1 g/m^2 daily x 5 for cytarabine and 40 mg/m^2 daily x 5 for clofarabine, we reported a response rate of 40% (28% complete remission) in 29 patients with a median age of 59 years (18 to 84 years). Responses extended to

patients with primary refractory disease and those with abnormal cytogenetics. Other groups have since followed this lead and published comparable results, albeit doses of cytarabine and clofarabine varied throughout the different studies.[7]

Anthracyclines have been traditionally combined with cytarabine in AML. Two recent publications highlighted higher response rates and better disease-free survival in both younger and older patients with frontline AML when high-dose daunorubicin (90 mg/m^2/dose) was used in a "3+7" induction combination highlighting the activity of this class of agents for AML therapy.[8-9] Pautas et al randomized 468 patients ages 50 to 70 years on Acute Leukemia French Association studies to 3 induction anthracycline regimens: idarubicin 12 mg/m^2 daily for 3 days, idarubicin 12 mg/m^2 daily for 4 days, and high-dose daunorubicin 80 mg/m^2 daily for 3 days. The CR rate with idarubicin daily for 3 days was higher than with high-dose daunorubicin (83% vs 70%), as was the 3-year event-free survival rate (23% vs 16%).[10]

The combination with nucleoside analogs synergizes the anthracyclines activity by inhibiting DNA repair damage. Holowiecki et al from Poland randomized 673 patients (ages 18 to 60 years) to receive either daunorubicin plus cytarabine (DA), or DA plus fludarabine, or DA plus chlorodeoxyadenosine (DAC). The authors reported significantly higher CR rates after 1 course of induction and overall and reported better 3-year survival rates with the addition of the DAC regimen.[11]

We have previously explored the combination of clofarabine, idarubicin, and cytarabine in a phase I study for patients with relapsed/refractory AML. The following doses were established for further evaluation: clofarabine 22.5 mg/m^2 daily x 5, idarubicin 6 mg/m^2 daily x 3, and cytarabine 0.75 mg/m^2 daily x 5.[12] In a recent update of a phase II study of 63 patients treated with CIA,[13] the overall response rate was 38% including 21% with complete remission. Median overall survival was 34 weeks for all patients and 66 weeks for those patients who achieved CR/CRp. Twenty-four patients (38%) were able to proceed with a stem cell transplant. Induction mortality was at 8%. Toxicities were manageable.

In view of this experience and in light of above data of the possible usefulness of higher doses of anthracyclines, and the synergistic activity of the combination of anthracyclines with nucleoside analogues, we propose to evaluate in a phase II Bayesian design the CIA combination at higher doses than established versus the FLAI combination in patients with relapsed/refractory and newly diagnosed AML (not fit for any protocol) and high-risk MDS.

III. BACKGROUND DRUG INFORMATION

A. Idarubicin:

Idarubicin is commercially available.

Mechanism of action:

Similar to doxorubicin and daunorubicin; inhibition of DNA and RNA synthesis by intercalation between DNA base pairs.

Adverse effects:

- Cardiovascular: Transient EKG abnormalities (supraventricular tachycardia, S-T wave changes, atrial or ventricular extrasystoles); generally asymptomatic and self-limiting. Congestive heart failure, dose-related. The relative cardiotoxicity of idarubicin compared to doxorubicin is unclear. Some investigators report no increase in cardiac toxicity at cumulative oral idarubicin doses up to 540 mg/m^2; other reports suggest a maximum cumulative intravenous dose of 150 mg/m2.

- Central nervous system: Headache

- Dermatologic: Alopecia (25% to 30%), radiation recall, skin rash (11%), urticaria

- Gastrointestinal: Nausea, vomiting (30% to 60%); diarrhea (9% to 22%); stomatitis (11%); GI hemorrhage (30%)

- Genitourinary: Discoloration of urine (darker yellow)

B. Cytarabine

Cytarabine is commercially available.

Mechanism of action:

Cytarabine is an antimetabolite. Cytarabine is cell cycle–specific for the S phase of cell division. Activity occurs as the result of activation to cytarabine triphosphate in the tissues and includes inhibition of DNA polymerase and incorporation of cytarabine into DNA and RNA.

Adverse effects:

COMMON

• Cardiovascular: Thrombophlebitis

• Dermatologic: Rash, conjunctivitis

• Endocrine metabolic: Hyperuricemia

• Gastrointestinal: Anal inflammation, Diarrhea, Loss of appetite, Nausea, Stomatitis, Ulcer of anus, Ulcer of mouth, Vomiting

• Hematologic: Decreased reticulocyte count, Megaloblastic anemia

• Hepatic: Decreased liver function

• Other: Fever

SERIOUS

• Hematologic: Anemia, Bleeding, Leukopenia, Thrombocytopenia

• Immunologic: Anaphylaxis

• Neurologic: Neuropathy

• Renal: Kidney disease

• Other: Infectious disease, Sepsis

C. Fludarabine

Fludarabine is commercially available.

Mechanism of action:

Fludarabine phosphate is fluorinated nucleotide and analog of antiviral agent vidarabine, that is relatively resistant to adenosine deaminase deamination. It is actively dephosphorylated to 2-fluoroara-A and phosphorylated further by deoxycytidine kinase to 2-ribonucleotide reductase and DNA primase resulting in DNA synthesis inhibition.

Adverse effects:

COMMON

• Endocrine metabolic: Shivering

• Gastrointestinal: Loss of appetite, Nausea, Vomiting

• Neurologic: Asthenia

• Other: Fatigue, Malaise

SERIOUS

• Cardiovascular: Edema (frequent)

• Dermatologic: Aplasia of skin (rare)

• Hematologic: Autoimmune hemolytic anemia, Graft versus host disease, Transfusion-associated, with non-irradiated blood (rare), Myelosuppression (frequent)

• Neurologic: Neurotoxicity

• Respiratory: Pneumonia (frequent)

• Other: Fever (frequent), Infectious disease

D. Clofarabine

Clofarabine is commercially available.

Mechanism of action:

Clofarabine potently inhibits DNA synthesis by inhibiting both DNA polymerase and ribonucleotide reductase. Clofarabine demonstrated the ability to disrupt mitochondrial integrity that results in the release of pro-apoptotic proteins, cytochrome C and apoptosis-inducing factor.

Adverse effects:

• Hematologic: Myelosuppression, infections

- Hepato and Gastrointestinal: Nausea/vomiting, diarrhea, mucositis, stomatitis/pharyngitis, hyperbilirubinemia, increase of SGPT and/or SGOT, abdominal pain or cramping, peritonitis, pancreatitis, liver failure

- Dermatologic: Skin rash with blisters (particularly hand-foot syndrome), Steven-Johnson's syndrome, alopecia, conjonctivitis

- Systemic: Fatigue, asthenia, anorexia, lethargy, malaise, mental status changes/coma, alopecia

- Allergic reactions: (including fever, muscle aches, edema, dyspnea)

- Cardiology: Congestive heart failure

- Nephrology: Kidney failure

- Autoimmune reactions: (antiplatelet antibodies, erythema nodosum) and/or chemical imbalances in the blood.

IV. Eligibility criteria

Inclusion criteria:

- Sign an IRB-approved informed consent document.

- Age 18 to 60. Patients above the age of 60 only with PI approval

- Diagnosis of newly diagnosed AML [other than acute promyelocytic leukemia (APL)]. Prior therapy with hydrea and the use of a single or a two day dose of cytarabine (up to 3 g/m^2) for emergency use up to 24 hours prior to start of study therapy is allowed. Prior therapy for MDS or other AHD is not allowed.

- ECOG performance status of ≤ 3 at study entry.

- Organ function as defined below (unless due to leukemia):

o   Serum creatinine ≤ 3 mg/dL

o   Total bilirubin ≤ 2.5 mg/dL

o   ALT (SGPT) ≤ 3 x ULN or ≤ 5 x ULN if related to disease

- Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days. Men must agree not to father a child and agree to use a condom if his partner is of child bearing potential.

- Cardiac ejection fraction ≥ 40% (by either cardiac echo or MUGA scan). Documentation of recent (≤ 6 months from screening) outside reports is acceptable.

Exclusion Criteria:

- Breast feeding females

- Patients with uncontrolled active infections (viral, bacterial, and fungal are not eligible).

- Patients with active secondary malignancy will not be eligible.

IV. Treatment plan

1. Study design

The study will include a phase I portion to determine MTD dose of clofarabine to be used in the subsequent randomized phase II portion. Patients will be randomized to either arm on an even basis at the beginning, then, based on efficacy and following a Bayesian design, patients will be assigned to the superior arm.

2. Induction

2.1 Phase I (fixed dose of idarubicin of 10 mg/m^2 day 1-3 and cytarabine 1 g/m^2 day 1-5)

Clofarabine IV over approximately 1 hour daily for 5 days (days 1-5). Dose levels and dose escalation schema are described below.

Idarubicin 10 mg/m^2 IV over approximately 30 minutes daily for 3 days (days 1-3)

Cytarabine 1 g/m^2 IV over approximately 2 hours daily for 5 days (days 1-5)

Idarubicin will follow clofarabine by 1 to 2 hours and cytarabine will follow clofarabine by 3 to 6 hours. All chemotherapeutic agents will be dosed, prepared, and administered according to MDACC institutional guidelines. BSA will be recalculated prior to each subsequent course.

Patients will be entered sequentially to each dose level. If none of the first 3 patients at a dose level experience first cycle dose-limiting toxicity (DLT), new patients may be entered at the next higher dose level. If 1 of 3 patients experience first cycle DLT, up to 3 more patients are started at that same dose level. If 2 or more experience first cycle DLT, no further patients are started at that dose and clofarabine's dose will be reduced to -1 level, which is 10 mg/m^2 IV daiy for 5 days. The MTD is the highest dose level in which <2 patients of 6 develop first cycle DLT. New dose levels may begin accrual only if all patients at the current dose level have been observed for a minimum of 4 weeks.

Dose escalation schedules are as follows:

Dose level	Clofarabine (mg/m^2 IV daiy for 5 days)
-1	10
1 Starting	15
2	20
3	25
4	30

A DLT is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first course on study that meets any of the following criteria:

- CTCAE Grade 3 AST (SGOT) or ALT (SGPT) for > 7 days

- CTCAE Grade 4 AST (SGOT) or ALT (SGPT) of any duration

- All other clinically significant NCI common terminology criteria that are CTCAE Grade 3 or 4

An AE must be clinically significant to define DLT e.g. alopecia, study drug-related fever, electrolyte abnormalities (including K, Na, Cl, HCO3, Mg, Ca) that are < Grade 3 will not define the DLT. Drug-related Grade 3-4 nausea and vomiting not controlled with adequate therapy and Grade 3-4 hyperbilirubinemia will be considered DLTs. Only prolonged myelosuppression, as defined by the NCI criteria specific for leukemia, i.e. marrow cellularity <5% on day 42 or later (6 weeks) from start of therapy without evidence of leukemia, will be considered in defining the MTD and DLT.

2.2 Phase II

In the Phase II portion, patients will randomized to receive

a. Clofarabine (dose selected based on Phase I portion) IV over approximately 1 hour daily for 5 days (days 1-5)

b. Idarubicin 10 mg/m^2 IV over approximately 30 minutes daily for 3 days (days 1-3)

c. Cytarabine 1 g/m^2 IV over approximately 2 hours daily for 5 days (days 1-5)

   Idarubicin will follow clofarabine by 1 to 2 hours and cytarabine will follow clofarabine by 3 to 6 hours.

   or

a. Fludarabine 30 mg/m^2 IV over approximately 30 minutes daily for 5 days (days 1-5)

b. Idarubicin 10 mg/m^2 IV over approximately 30 minutes daily for 3 days (days 1-3)

c. Cytarabine 1 g/m^2 IV over approximately 2 hours daily for 5 days (days 1-5)

   Idarubicin will follow fludarabine by 1 to 2 hours and cytarabine will follow fludarabine by 3 to 6 hours.

The induction or reinduction may be given over 4 days (Fludarabine, Clofarabine and Cytarbine) in patients ≥ 65 years, or at the discretion of the treating physician and over 3 days (Fludarabine, Clofarabine and Cytarbine) in patients with PS ≥ 2, or at the discretion of the treating physician. Idarubicin 8-10 mg/m^2 will be given for 2 days in these situations.

Patients, who have not achieved a complete remission following one induction course can receive a second induction course to optimize response if possible. A second induction course at the same dose as the previous course or in a dose-reduced fashion

should not be given until at least 28 days of course 1. If the bone marrow aspirate and/or biopsy(s) performed after the re-induction cycle reveals a remission marrow (CR/CRp), then the patient may proceed with consolidation at the discretion of the treating investigator. In addition, any clinically significant drug-related, non-hematologic toxicity experienced by a patient should return to ≤ grade 2 or the baseline grade before the patient continues treatment. Should the patient not have achieved a remission after the reinduction course, he will be taken off study for failure to respond, unless the patient has achieved clinical benefit or partial remission, at which time further therapy on protocol may be permitted with approval from the PI.

Consolidation

Patients in CR or CRp can continue with up to 6 consolidation cycles.

Clofarabine (dose selected based on Phase I portion) IV over approximately 1 hour daily for 3 days (days 1-3)

Idarubicin 8 mg/m^2 IV over approximately 30 minutes daily for 2 days (days 1-2)

Cytarabine 1 g/m^2 IV over approximately 2 hours daily for 3 days (days 1-3)Or

Fludarabine 30 mg/m^2 IV over approximately 30 minutes daily for 3 days (days 1-3)

Idarubicin 8 mg/m^2 IV over approximately 30 minutes daily for 2 days (days 1-2)

Cytarabine 1 g/m^2 IV over approximately 2 hours daily for 3 days (days 1-3)

The consolidation may be given over 2 days in patients ≥ 65 years and/or with PS ≥ 2.

Cycles may be repeated every 3 to 10 weeks based on leukemia response and resolution of drug-related toxicities. Prior to each consolidation cycle, the ANC should be $\geq$ 1.0 x 10^9/L, and the platelet count should be $\geq$ 60 x 10^9/L (except for patients who are considered to have achieved a CRp following induction/reinduction and in whom the platelet count may be lower). Patients with borderline values for ANC and platelet count (value up to 10% lower than recommended) can still proceed with the next consolidation cycle if this is judged to be in the best interest of the patients and after discussion with the principal investigator. In addition, any drug-related non-hematologic toxicity experienced by the patient must return to $\leq$ grade 2 before receiving the next cycle. Doses missed or held during a cycle of treatment will not be made up and are recorded as being omitted. If patients experience multiple study drug-related toxicities or experience significant infections, dose adjustments may need to be made based on the most severe toxicity and based on the drug causing the toxicity.

Dose modifications:

Drug doses in subsequent consolidation cycles may be modified for drug-related > grade 2 non-hematologic toxicities. Dose reductions can also be made in other clinical situations where this step is considered to be in the best interest for the patient and after discussion with the principal investigator. The following table is a suggestion for dose modifications in subsequent treatment courses:

Dose level	Fludarabine (mg/m^2)	Clofarabine (mg/m^2)	Idarubicin (mg/m^2)	Cytarabine (g/m^2)
-1	22.5	15	8	0.75
-2	20	15	6	0.5

-3	15	10	6	0.25

Doses of each individual drug can be modified if a toxicity is considered due this

particular drug.

Specific Dose Modifications for Organ Function:

	Fludarabine (mg/m^2)	Cytarabine (g/m^2)	Idarubicin (mg/m^2)	Clofarabine (mg/m2)
Creatinine (mg/dL)				
2.1 – 3 (age < 65)	22.5	0.75	10 * 8 **	75% of current dose level
2.1 – 3 (age ≥ 65)	15	0.5	8 * 6 **	50% of current dose level
Above 3	Discuss with study principal investigator			
Bilirubin (mg/dL)				
2.6 – 5	30	1	5 * 4 **	Current dose level
Above 5	30	1	OMIT	Current dose level

*Induction/Re-Induction   **Consolidation

V. PRETREATMENT AND POST-TREATMENT EVALUATION

Induction Treatment (Pre-treatment)

1. CBC, diff, platelet count.

2. Creatinine, bilirubin, ALT or AST, marrow aspirate with cytogenetics (if bone

   marrow not done within 1 month or cytogenetics within 3 months. For patients

   with evidence of leukemia in the peripheral blood, the bone marrow may be

   omitted after discussion and approval with the principal investigator.)

Pretreatment Evaluation

Procedure	Comments	Schedule
Informed Consent	Obtain standard informed consent approved by IRB	Within 14 days of therapy
Medical History	History of present illness, known allergies, prior cancer history as far as traceable, and past medical/ surgical history as far as relevant.	Within 14 days of therapy
Physical Examination	Vital signs (temperature, heart rate, respiratory rate, blood pressure) and performance status.	Within 14 days of therapy
Concomitant	Document concomitant medications	Within 14 days

Procedure	Comments	Schedule
Medications		of therapy
Hematology	CBC with differential and platelet count	Within 14 days of therapy
Biochemistry	Creatinine, total bilirubin, SGPT or SGOT	Within 14 days of therapy
Bone marrow	Aspirate and/or biopsy[*] Cytogenetics	Within 30 days of therapy Within 90 days of therapy
Pregnancy test	Serum or urine, if female *and* of child-bearing potential only	Within 7 days of therapy

- For patients with evidence of leukemia in the peripheral blood, the bone marrow may be omitted after discussion and approval with the PI.

During therapy

1. CBC, differential, and platelet count every 3-7 days (the differential may be omitted when the WBC is $\leq$ 500.)

2. Creatinine, bilirubin, ALT or AST once weekly.

3. Marrow aspirate to confirm complete remission.

During Therapy

Procedure	Comments	Schedule
Hematology	CBC with differential and platelet count	Every 3-7 days (the differential may be omitted when WBC is ≤500)
Biochemistry	Creatinine, total bilirubin, SGPT or SGOT	Once weekly
Physical Examination	Focused physical examination	Prior to each treatment course
Bone marrow	Aspirate and/or biopsy	On day 28 +/- 7 days

During Post-Remission Therapy

CBC, diff, platelet count, creatinine, and bilirubin prior to each post-CR course. Marrow aspirates every 2-3 cycles.

Targeted Therapy

Patients with AML may harbor FLT3/ITD mutations. We have previously explored the use of sorafenib in these patients and was found to be safe and therefore we can allow patients with FLT3/ITD mutations to receive concomitant sorafenib therapy at a dose of 400 mg orally twice daily continuously at the discretion of the treating physician.

In addition patients with Acute Myeloid Leukemia may evolve from Myeloid Fibrosis where JAK2 inhibitors such as ruxolitinib was found to be effective therefore we will allow the concomitant use of ruxolitinib @ 20 mg BID at the discretion of the treating physician.

Patients with the presence of BCR/Abl or the Philadelphia chromosome may receive concomitant therapy with any approved TKI. TKI therapy will be given orally and should be given continuously. The choice and the dose will be at the discretion of the investigator.

Supportive care

Supportive measures such as prophylaxis for tumor lysis syndrome, erythropoietin, analgesics, blood transfusions, antimicrobials and hematopoietic colony stimulating factors for treatment of cytopenias are permitted. The administration of anti-leukemia therapies is not permitted, except for hydroxyurea which is allowed for up to 7 days each during cycle 1-3 and the use of a single or a two day dose of cytarabine (up to 3 g/m^2) for emergency use up to 24 hours prior to start of study therapy. Intrathecal chemotherapy is allowed for patients with CNS disease.

VI. STUDY END POINTS

Primary:

1. Complete remission rates with the 2 different regimens

Secondary:

1. Event free survival at 2 years (events defined as death and relapses)

2. Overall survival

3. Remission duration

4. Predictive factors for response and outcome

5. Safety profile

VII. CRITERIA FOR WITHDRAWAL

Reasons for withdrawal include:

• withdrawal of consent or the subject refuses to continue treatment and/or

procedures/observations.

• relapse unless the treating physician determines that the patient has achieved clinical

benefit, at which time further therapy on protocol may be permitted with approval from

the PI.

• failure to achieve at least a CRi after 2 induction courses

VIII. CRITERIA FOR RESPONSE

The response criteria recommended by the NCI and the MDS International Working

Group.

Definitions:

Complete Response (CR):

Neutrophil count ≥ 1.0 ×10^9/L

Platelet count ≥ 100 ×10^9/L

• Bone marrow aspirate </= 5% blasts

No extramedullary leukemia

CRi:

• Response as in CR but platelets <100 ×10^9/L

Partial response (PR):

Neutrophil count ≥ 1.0 ×10^9/L

Platelet count ≥ 100 ×10^9/L

≥ 50% reduction in bone marrow blasts over baseline

Clinical benefit:

In addition to IWG criteria, in AML, a decrease in bone marrow blasts to <5% will also

be considered clinical benefit.

Stable Disease:

In addition to IWG criteria and in absence of any of the above response criteria, patients

will be considered to have stable disease if the bone marrow blast percent does not

increase compared to pretreatment level.

Relapse:

Increase of bone marrow blasts to > 10% after an initial response.

IX. REPORTING REQUIREMENTS

All adverse and serious adverse events will be recorded and reported according to the

Department of Leukemia guidelines (appendix D)

X. STATISTICAL CONSIDERATIONS

This is a phase I/II study of CIA and FIA in patients with relapsed/refractory and newly diagnosed AML (not fit for any other protocol) and high-risk MDS. The objective of the phase I study is to determine the safety profile and MTD of the combination therapy of CIA. The Objective of the phase two study is to compare the response rate of the two combination regimens CIA and FLAI.

Phase I

First, phase I study is performed to assess the safety of the combination therapy of CIA. Four combination dose levels are defined. A 3+3 design will be used to for dose escalation. Detailed dose escalation rules are described in the section 2.1 of the protocol. A maximum of 24 patients will enroll in the phase I study.

Phase II

The phase II portion of the study will include only newly diagnostic AML patients, and the primary objective is to compare the event-free survival (EFS) between treatment CIA and FLAI, where event is defined as be resistance to treatment, relapse (after response) or death, whichever occurred first.

A maximum of 200 front-line patients will be enrolled in the study. To enroll 200 front line patients, the total sample size (front-line and salvage patients combined) is 280. This section will focus on front-line patients only. An adaptive randomization algorithm will be used to assign the patients to the two treatment arms. Initially 40 patients will be randomized equally to the two treatment arms. After the completion of the equal randomization, the adaptive randomization algorithm will be employed to unbalance the

randomization probabilities in favor of the treatment arm with a better event free survival. The expected accrual rate is about 5 patients per month, and the additional follow-up time is 12 months after all patients have been enrolled to the study.

The historical data suggested the median event free survival time for FLAI treatment was 5 months. Let θ_1 and θ_2 denote the median event free survival time for treatment arm CIA and FLAI respectively, we assume the prior for the median event free survival time follows Inverse Gamma (IG) distribution: $\theta_1 \sim$ IG(3, 10), and $\theta_2 \sim$ IG(3, 10). Each time a new patient enters the trial, be the posterior probabilities $\pi_i = Pr(\theta_i > \theta_j \mid data)$ will be calculated (i, j = 1,2). The randomization probability to treatment arm CIA and FLAI will be the posterior probabilities $\pi_i = \frac{\sqrt{\pi i}}{\sqrt{\pi 1} + \sqrt{\pi 2}}$.

The trial will be stopped early for both efficacy and futility based on the follow stopping rules. Table 1 presents the operating characteristics of simulations based on the described design.

1. Early loser selection: Suspend accrual to an arm I if $Pr(\theta_I < \theta_{j \neq I} \mid Data) < 0.025$

2. Early winner selection: Stop the trial and select an arm i as superior if $Pr(\theta_i > \theta_{j \neq i} \mid Data) > 0.975$

3 Final winner selection: At the final analysis after all patients have been evaluated, select arm i as superior if $Pr(\theta_i > \theta_{j \neq i} \mid Data) > 0.975$

Table 1: Operating characteristics from simulations

	Arm	True Median Survival (M)	Pr(Selected)	Pr(Selected Early)	Pr(Stopped Early)	# Patients (2.5%, 97.5%)
Scenario 1	Arm1	5	0.12	0.116	0.111	88.2 (20, 137)
	Arm2	5	0.111	0.106	0.12	87.1 (20, 135)
Scenario 2	Arm1	2	0	0	1	22.5 (20, 35)
	Arm2	5	1	1	0	27.7 (20, 64)
Scenario 3	Arm1	7	0.757	0.718	0.014	74.8 (20, 140)
	Arm2	5	0.014	0.014	0.757	50.6 (20, 110)
Scenario 4	Arm1	8	0.937	0.909	0.001	62.3 (20, 134)
	Arm2	5	0.001	0.001	0.937	40 (20, 90)
Scenario 5	Arm1	10	0.995	0.992	0.001	43.7 (20, 109)
	Arm2	5	0.001	0.001	0.995	30.5 (20, 66)

Toxicity monitoring

Toxicity will be monitored closely for each treatment arm using the method of Thall et al

(1995). Denote the probability of toxicity by P_E, where toxicity is defined as any

treatment-related grade 3 or greater non-hematological toxicities. We assume $P_E \sim$

beta (0.6, 1.4). We will stop the trial if at any point Pr ($P_E > 0.30$ | data) >0.95. That is,

we will stop the trial if, at any time during the study, we determine that there is more

than 95% chance that the toxicity rate is more than 30%. The trial will be stopped if (the

number of toxicity observed / among number of patients) ≥ 6/10, 11/20, 15/30, 19/40,

22/50, 26/60, 30/70, 34/80, 38/90, 42/100, 46/110, 49/120, 53/130.   The operating

characteristics are listed in table 2.

Table 2: The operating characteristics for toxicity monitoring are summarized in the following table

True toxicity probability	Probability of early stop	Sample size percentiles (10, 25, 50, 75, 90)
0.1	0.0002	140 140 140 140 140
0.2	0.008	140 140 140 140 140
0.3	0.095	140 140 140 140 140
0.4	0.666	10 30 70 140 140
0.5	0.995	10 10 20 40 60

AdaptiveRandomization 4.1.1 software and Multic99 were used for the trial design.

Analysis method

Data analysis will be performed using SAS or S-plus, as appropriate. The median EFS time will be estimated by Bayesian posterior estimates, along with the 95% credible intervals for both treatment arms. The posterior probability that one arm has a better EFS than the other arm will be also calculated.

Demographic and baseline laboratory results will be summarized using descriptive statistics, including means with standard deviations, or medians with ranges, histograms and box-plot. Fisher's exact test and Wilcoxon rank test will be used in the data analyses of categorical and continuous variables, respectively. Survival or times to failure and time to progression functions will be estimated using the Kaplan-Meier method. The two-sided log-rank test will be used to assess the differences of time to events between groups, and Cox proportional hazards model will also be fitted to compare the time-to-event outcomes between the two treatment arms adjusting for the effects of covariates. Toxicity will be reported by type, frequency and severity. Highest toxicity grades per patient per course will be tabulated for selected adverse events and laboratory measurements.

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