



Protocol Page

Phase I/II Study of Decitabine (DAC) followed by Clofarabine, Idarubicin, and Cytarabine (CIA) in Acute Leukemia
2012-1064

Core Protocol Information

Short Title	Decitabine followed by Clofarabine, Idarubicin, and Cytarabine in Acute Leukemia
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Which Committee will review this protocol?

- The Clinical Research Committee - (CRC)

Protocol Body



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**Phase I/II Study of Decitabine (DAC) followed by Clofarabine,
Idarubicin, and Cytarabine (CIA) in Acute Leukemia**

1. OBJECTIVES

Phase I

Primary:

To determine the maximal tolerated dose (MTD) of clofarabine to be used in portion II of the study

Phase II

Primary:

To determine the response rate of the DAC-CIA regimen

Secondary:

A) To determine the toxicity of the combination regimen

B) To determine the disease-free survival (DFS) and overall survival (OS) rates

2. RATIONALE

2.1 Acute Myelogenous Leukemia

Acute myelogenous leukemia (AML) is the most common acute leukemia in adults. It is estimated that 13,780 men and women will be diagnosed with and 10,200 men and women will die of acute myeloid leukemia in the year 2012.¹ AML is a disease with a poor prognosis with a 5-year survival of only around 30%.^{2,3} Certain subgroups of AML have a particularly worse

outcome such as patients with relapsed and/or refractory AML and AML arising from antecedent myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPNs).

Although most patients with AML will achieve remission with induction chemotherapy; many patients will relapse, despite the administration of post-remission therapies. Relapses may occur weeks to many years later. Up to 10% of patients will be refractory to induction chemotherapy. Both of these groups of patients (relapsed/refractory) constitute a particularly poor risk group. Although an allogeneic stem cell transplant would be considered a recommended approach for most of these patients, it is feasible only in a small number of patients. Many novel drugs and approaches are being investigated for this group of patients. However, the CR rates have been, in general, less than 30%.⁴⁻⁶ The Eastern Cooperative Oncology Group (ECOG) conducted a randomized 3-arm phase II trial where relapsed/refractory AML patients received either intermediate-dose cytarabine/gemtuzumab ozogamicin, or intermediate-dose cytarabine/liposomal daunorubicin, or intermediate-dose cytarabine/ cyclophosphamide/ topotecan.⁴ The CR/CRp (CR with incomplete platelet count recovery) rates achieved were low, ranging from 4% to 12%, depending on the study arm. Cortes et al. performed an exploratory study in relapsed/refractory AML patients combining p53 antisense oligonucleotide Cenersen with idarubicin either alone or with cytarabine.⁵ Ten of the 53 (19%) patients achieved CR/CRp. These data highlight the need for development of better treatment strategies for this group of patients.

AML arising from antecedent MDS/MPN: In a recent study by Bello and colleagues, outcomes of patients who progressed from MDS were studied.⁷ In the subgroup of patients who had failed hypomethylating agents (the current FDA approved standard therapy for MDS), the median overall survival (OS) was only 3.7 months from the time of AML diagnosis. Those with poor

risk cytogenetics (very common for this group of patients) had median OS of only 2.8 months. In our experience, the outcomes of these patients remains dismal with CR rate in <20% range (Jabbour et al. MDACC, unpublished data). Given these poor outcomes with the conventional treatment approaches, we plan to include these patients for frontline treatment of the AML.

2.2 Combination chemotherapy for AML: Emerging role of purine analogs

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/m²/dose) was used in a “7+3” induction combination highlighting the activity of this class of agents for AML therapy.^{8,9} Pautas et al randomized 468 AML patients ages 50 to 70 years to 3 induction anthracycline regimens: idarubicin 12 mg/m² daily for 3 days, idarubicin 12 mg/m² daily for 4 days, and high-dose daunorubicin 80 mg/m² daily for 3 days.¹⁰ The CR rate with idarubicin daily for 3 days was higher than with high-dose daunorubicin (83% vs. 70%). A recent report from the Polish Acute Leukemia Group provides evidence for adding purine analog cladribine to the standard daunorubicin plus cytarabine regimen.¹¹ In a phase III study, 652 untreated patients (ages 18 to 60 years) with AML were randomized to receive either daunorubicin plus cytarabine (DA), or DA plus fludarabine, or DA plus cladribine. The CR rate was significantly higher in the cladribine arm compared to the DA arm (67.5% vs. 56%; p=0.01). The OS was also better in the cladribine arm compared to DA arm (3-year OS: 45% vs. 33%, p=0.02). The survival advantage of the cladribine arm over the DA arm was observed among patients age 50 years or older (p=0.005), those with initial leukocyte count above 50 x 10⁹/L (p=0.03), and those with unfavorable karyotype (p=0.03).

2.3 Clofarabine in AML

Clofarabine (2-chloro-2-fluoro-deoxy-9-β-D-arabinofuranosyladenosine) is a second-generation nucleoside analog, which was developed as a hybrid molecule to combine the most favorable pharmacokinetic properties of both fludarabine and cladribine and has better stability with higher affinity to deoxycytidine kinase, the rate-limiting step in phosphorylation of nucleosides.¹²

Clofarabine acts as an inhibitor of both DNA synthesis and the enzyme ribonucleotide reductase (RNR). Its structural characteristics render it resistant to deamination by adenosine deaminase and phosphorolytic cleavage by bacterial purine nucleoside phosphorylase.¹³⁻¹⁶ Single agent clofarabine has demonstrated activity in phase I-II studies in AML.^{17,18} 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 cytarabine in AML.¹⁹ We have previously conducted a study combining cytarabine with clofarabine in patients with relapsed/refractory AML.²⁰ At doses of 1 g/m² daily x 5 days for cytarabine and 40 mg/m² daily x 5 days 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.²¹ We have also reported adaptively randomized study of lower-dose clofarabine (30mg/m² IV daily for 5 days) with or without low-dose cytarabine (20mg/m² SQ daily for 14 days) in previously untreated older (≥60 years) with AML. CR rate was significantly higher with the combination therapy (63% vs. 31%; p=0.025). The combination arm also had improved event free survival (7.1 months vs. 1.7 months; p=0.04), but not overall survival (11.4 months vs. 5.8 months; p=0.1). No excess toxicity was observed in the combination arm. We have previously explored

the combination of clofarabine with cytarabine and anthracycline (CIA regimen). In a phase I study for patients with relapsed/refractory AML, the following doses were established for further evaluation: clofarabine 22.5 mg/m² daily x 5 days, idarubicin 6 mg/m² daily x 3 days, and cytarabine 0.75 mg/m² daily x 5 days.²² In a recent update of a phase II study of 63 patients treated with CIA regimen,²³ the overall response rate was 38% including 21% CR. 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.

2.4 The role of Hypomethylating agents in AML

In the last decade there has been an increasing recognition of the important pathogenetic role of epigenetic changes in leukemogenesis.²⁴ Aberrant DNA methylation of tumor suppressor genes, leading to their inactivation is an important step in carcinogenesis.²⁵ Thus, drugs such as DNA methyltransferase inhibitors which lead to DNA hypomethylation may lead to reexpression of tumor suppressor genes. Two such agents, 5-azacytidine and decitabine are currently approved by the United States Food and Drug Administration for the treatment of MDS and have demonstrated single-agent activity in AML patients.²⁶⁻²⁹

Kantarjian et al. performed a multicenter, randomized, open-label, phase III trial comparing the efficacy and safety of decitabine with treatment choice (TC, supportive care or cytarabine 20 mg/m² per day subcutaneously for 10 consecutive days every 4 weeks) in older patients (age ≥65 years) with newly diagnosed AML and poor- or intermediate-risk cytogenetics.²⁶ Patients (n=485) were randomly assigned 1:1 to receive decitabine 20 mg/m² per day as a 1-hour intravenous infusion for five consecutive days every 4 weeks or TC. The primary analysis

showed a nonsignificant increase in median OS with decitabine (7.7 months; 95% CI, 6.2 to 9.2) versus TC (5.0 months; 95% CI, 4.3 to 6.3; p=0.108). Based on this trial results, on September 28, 2012, the European Commission approved decitabine for the treatment of adult patients (age 65 years and above) with newly diagnosed AML, who are not candidates for standard induction chemotherapy.

2.5 Combination of hypomethylating agents and chemotherapy in AML

There is preclinical evidence that DNA hypomethylating agents can sensitize tumor cells to cytotoxic chemotherapy.³⁰⁻³⁴ Studies in the late 1970's showed that combination of 5-azacytidine and cytarabine was synergistic both in vitro and in vivo, when used sequentially whereas concurrent administration was antagonistic.³⁵ These studies were, however, done using higher doses of 5-azacytidine (600-1500 mg/m² per course), which led to significant non-hematologic toxicities in these earlier clinical trials.³⁶ It is now known that the effects of 5-azacytidine and decitabine on DNA hypomethylation occur at a significantly lower dose range; and the standard dose of decitabine is 20mg/m² daily for 5 days.³⁷⁻⁴⁰ Qin et al. reported the synergism of decitabine at clinically relevant doses with cytarabine in the HL-60 AML cell line.³⁴ The authors showed that hypomethylated cells following treatment with decitabine were more likely to undergo apoptosis when treated with cytarabine. Scandura et al. recently reported outcomes of 30 untreated younger (\leq 60 years old) patients with intermediate/poor risk AML who received decitabine as a 'priming' agent prior to the conventional '7+3' chemotherapy.⁴¹ Overall CR rate of 83% was noted (57% with first induction). No excess toxicity was noted with the decitabine priming approach and the toxicity profile was similar to the standard induction. Though there was a prior concern for potential prolonged myelosuppression with this approach, the authors, on

the contrary found faster platelet recovery (median 22 days) with the decitabine ‘priming’ compared to their prior experience with cytarabine-containing induction regimens.⁴¹ The German group has reported preliminary results of a dose-finding study in which 5-azacytidine was used at 2 different dosing regimen (75mg/m² and 37.5mg/m²) immediately prior to standard induction with ‘7+3’.⁴² In their preliminary analysis, the tolerability of the 2 arms was similar and they have selected 75mg/m² dose (the standard dosing for 5-azacytidine) as the phase II dose.

Based on these observations, we hypothesize that addition of decitabine to our current standard chemotherapy regimen (clofarabine, idarubicin, cytarabine), the DAC-CIA regimen, would be synergistic and would ultimately lead to an improvement in CR rates and patient outcomes. We propose a phase I-II study. The primary endpoint of the phase I study is to determine the maximal tolerated dose (MTD) of clofarabine to be used in the phase II portion of the study. The primary endpoint of the phase II study is to determine the response rate of DAC-CIA regimen.

2.6 Acute Lymphoblastic Leukemia (ALL)

Patients with relapsed/Refractory ALL constitute a poor risk group with dismal long-term outcomes. Fielding and colleagues analyzed the outcomes of 609 relapsed adult ALL patients who were treated on the MRC trial.⁴³ The median OS was only 5.5 months with the 5-year OS of only 7%. Similar poor outcomes of relapsed patients with ALL have been reported by the French and PETHEMA groups.^{44,45} Thus, patients with relapsed ALL continue to be a challenging subgroup of patient and novel treatment strategies are indicated.

Epigenetic dysregulation is now thought to play an important role in pathogenesis of ALL.⁴⁶

Promoter hypermethylation of cancer related genes such as Wnt, Src and others have been shown

to be an independent prognostic marker for poor survival in ALL patients.⁴⁷⁻⁴⁹ Preclinical evidence supports use of hypomethylating agents such as decitabine in ALL patients.^{46,50} In the proposed clinical trial, all the chemotherapy drugs (clofarabine, idarubicin, cytarabine) have been shown to have independent anti-leukemic activity in ALL.^{17,51,52} Therefore, the proposed regimen (decitabine followed by the CIA chemotherapy) deserves evaluation as a treatment strategy for relapsed/refractory ALL patients. We plan to enroll ALL patients only in the phase II part of the study.

3. BACKGROUND DRUG INFORMATION

3.1. 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/m²; 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)

3.2. 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

3.3. 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), alopecia, Steven-Johnson's syndrome
- Systemic: Fatigue, asthenia, anorexia, lethargy, malaise, mental status changes/coma, alopecia
- Allergic reactions: fever, muscle aches, edema, dyspnea
- Cardiology: Congestive heart failure
- Nephrology: Kidney failure
- Autoimmune reactions: antiplatelet antibodies, erythema nodosum

3.4. Decitabine

Decitabine is commercially available.

Mechanism of action:

Decitabine is a nucleoside analog. It is metabolized intracellularly by the enzyme deoxycytidine kinase and gets incorporated into DNA. It is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. Hypomethylation may restore normal function to genes that are critical for differentiation and inhibition of proliferation.

Adverse effects:

Myelosuppression, nausea/vomiting, diarrhea, mucositis, skin rash, fatigue, mental status changes/coma, allergic reactions (including fever, muscle aches, edema, dyspnea), congestive heart failure, liver failure, kidney failure, infections, lethargy, malaise, asthenia, alopecia, peritonitis, anorexia, stomatitis/pharyngitis, hyperbilirubinemia, increase of SGPT and/or SGOT, abdominal pain or cramping.

Also reported on decitabine trials, but with the relationship to decitabine still undetermined: allergic reaction, allergic rhinitis, GVHD, atrial fibrillation, cardiac ischemia/infarction, cardiopulmonary arrest, hypotension, left ventricular systolic dysfunction, right ventricular dysfunction, fever, insomnia, rigors/chills, weight loss, pruritus, rash, anal ulcer, ascites, constipation, abdominal distention, esophagitis, GI obstruction, ileus, taste alteration, CNS hemorrhage, GI hemorrhage, lung hemorrhage, nose hemorrhage, petechiae, urinary hemorrhage, cholecystitis, liver failure, infection without neutropenia, opportunistic infection, perianal abscess, head/neck edema, alkaline phosphatase, creatinine, hypercalcemia, hyponatremia,

fracture, agitation, CNS ischemia, confusion, depression, dizziness, extrapyramidal/involuntary movement, motor neuropathy, psychosis, seizure, sensory neuropathy, bone pain, headache, muscle pain, urinary pain, ARDS, bronchospasm, cough, dyspnea, hiccups, pneumonitis/pulmonary infiltrates, cystitis.

4. ELIGIBILITY CRITERIA

Inclusion criteria:

- Sign an IRB-approved informed consent document.
- Age ≥ 18 to 65 years.
- Diagnosis of AML [other than acute promyelocytic leukemia] with refractory/relapsed disease (Patients must be either primary refractory, in relapse 1, or in relapse 2).

NOTE: Patients with AML arising from prior MDS or MPN will be eligible even if they have not received treatment for the AML.

NOTE: Patients with relapsed/refractory ALL will also be eligible for the phase II part of the study.

NOTE: Use of hydroxyurea and/or up to 4 doses of cytarabine, for emergent cytoreduction is allowed

- ECOG performance status of ≤ 2 at study entry.
- Organ function as defined below (unless due to leukemia):
 - Serum creatinine ≤ 3 mg/dL
 - Total bilirubin ≤ 2.5 mg/dL
 - ALT (SGPT) ≤ 3 x ULN or ≤ 5 x ULN if related to disease
- Cardiac ejection fraction $\geq 40\%$ (by either cardiac ECHO or MUGA scan)

- 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.

Exclusion Criteria:

- Breast feeding women
- Patients with uncontrolled active infections (viral, bacterial, and fungal are not eligible).
- Patients with active secondary malignancy will not be eligible unless approved by the PI.
- NOTE: Prior therapy with decitabine, clofarabine, idarubicin, or cytarabine is allowed, unless the prior therapy is identical to the schema/schedule proposed in this study

5. TREATMENT PLAN

5.1. Study design

The study will include a phase I portion to determine MTD dose of clofarabine to be used in the subsequent phase II portion. Starting with Dose level 1, the patient will be enrolled by cohort of 3. Once the DLT assessment for the 3 patients is completed, a sequential of another cohort of 3 patients will be enrolled. If at any time, we see more than 30% patients experiencing DLT, we will de-escalate to dose level (-1). The same above monitoring rule will also be applied to dose level -1. A total of 18 patients will be enrolled. Once the phase II dose of clofarabine is established, additional patients will be enrolled in the phase II portion of the study.

5.2. Induction

5.2.1 Phase I (fixed dose of decitabine 20mg/m² days 1-5, idarubicin 10 mg/m² days 6-8 and cytarabine 1 g/m² days 6-10)

Clofarabine 15 mg/m² IV over approximately 1 hour daily.

Dose levels and dose escalation schema are described below.

Dose level	Clofarabine 15 mg/m²/day IV daily
-1	Clofarabine daily for 3 days (days 6-8)
1	Clofarabine daily for 4 days (days 6-9)

Decitabine 20 mg/m² IV over approximately 1 hour daily for 5 days (days 1-5)

Idarubicin 10 mg/m² IV over approximately 30 minutes daily for 3 days (days 6-8)

Cytarabine 1 g/m² IV over approximately 2 hours daily for 5 days (days 6-10)

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.

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 total bilirubin or AST (SGOT) or ALT (SGPT) for > 7 days
- CTCAE Grade 4 total bilirubin or 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. Prolonged myelosuppression, as defined by the NCI criteria specific for leukemia, i.e. marrow cellularity <5% on day 42 or later from start of therapy without evidence of leukemia, will be considered as DLT. All other prolonged myelosuppressions will also be monitored closely. Note: As the patients receive 5-days of decitabine therapy prior to starting the induction chemotherapy, extra 5-days will be allowed to assess for prolonged myelosuppression. In addition to the above, patient death will be monitored closely. Any death will be submitted to discussion by the Department of Leukemia meeting.

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 33 days of course 1, unless an earlier administration is judged to be in the best interest of the patient by the treating physician. If the bone marrow aspirate and/or biopsy(s) performed after the re-induction cycle reveals a remission marrow (CR/CRp/CRi), then the patient may proceed with consolidation at the discretion of the treating physician. 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 (CR/CRp/CRi) 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.

5.2.2 Phase II

In the Phase II portion, patients will receive the following treatments

Clofarabine 15 mg/m² IV over approximately 1 hour daily (number of days selected based on Phase I portion).

Decitabine 20 mg/m² IV over approximately 1 hour daily for 5 days (days 1-5)

Idarubicin 10 mg/m² IV over approximately 30 minutes daily for 3 days (days 6-8)

Cytarabine 1 g/m² IV over approximately 2 hours daily for 5 days (days 6-10)

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, 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 33 days of course 1, unless an earlier administration is judged to be in the best interest of the patient by the treating physician. If the bone marrow aspirate and/or biopsy(s) performed after the re-induction cycle reveals a remission marrow (CR/CRp/CRi), then the patient may proceed with consolidation at the discretion of the treating physician. In addition, any clinically significant drug-related, non-hematologic toxicity experienced by a patient should return to \leq grade 2 or the baseline grade before the patient continues treatment. Should the patient not have

achieved a remission (CR/CRp/CRi) 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.

5.3 Consolidation (for both phase I and phase II portion)

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

Decitabine 20 mg/m² IV over approximately 1 hour daily for 5 days (days 1-5)

Clofarabine 15 mg/m² IV over approximately 1 hour daily for 3 days (days 6-8)

Idarubicin 8 mg/m² IV over approximately 30 minutes daily for 2 days (days 6-7)

Cytarabine 1 g/m² IV over approximately 2 hours daily for 3 days (days 6-8)

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 $> 1.0 \times 10^9/L$, and the platelet count should be $> 60 \times 10^9/L$ (except for patients who are considered to have achieved a CRp or CRi 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.

5.4 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	Decitabine (mg/m²)	Clofarabine (mg/m²)	Idarubicin (mg/m²)	Cytarabine (g/m²)
0	20	15	8	1
-1	20	12.5	8	0.75
-2	20	12.5	6	0.5
-3	20	10	6	0.25

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

Specific Dose Modifications for Organ Function:

	Decitabine (mg/m²)	Cytarabine (g/m²)	Idarubicin (mg/m²)	Clofarabine (mg/m²)
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Creatinine (mg/dL)				
2.1 – 3.0 (age <65)	20	0.75	10 (induction) 8 (consolidation)	75% of current dose level
2.1 – 3.0 (age ≥65)	20	0.5	8 (induction) 6 (consolidation)	50% of current dose level
>3.0	Discuss with Study PI			
Bilirubin (mg/dL)				
2.6 – 5.0	20	1	5 (induction) 4 (consolidation)	Discuss with Study PI
>5.0	20	1	OMIT	Discuss with Study PI

6. PRETREATMENT AND POST-TREATMENT EVALUATION

Pre-treatment evaluation

- Medical history, physical examination and concomitant medication within 14 days of treatment start
- CBC, differential, platelet count and chemistry panel (at least including BUN, creatinine, SGPT and/or SGOT, total bilirubin, LDH, electrolytes, uric acid) within 7 days of treatment start

- Bone marrow aspirate and/or biopsy with appropriate flow cytometry within 1 month of treatment start (and cytogenetic evaluation within 3 months of treatment start). For patients with evidence of leukemia in the peripheral blood, the bone marrow may be omitted after discussion and approval with the principal investigator.
- Echocardiography or MUGA scan to assess cardiac ejection fraction within 8 weeks of treatment start
- For women of childbearing age, a negative serum and/or urine pregnancy test is required within 7 days of treatment start

Evaluation during study

- Physical exam prior to every cycle.
- CBC, differential, and platelet count twice weekly during induction and reinduction then at least weekly during consolidation. The differential may be omitted when the WBC count is $\leq 500/\mu\text{L}$.
- Chemistry panel (at least including electrolytes, BUN, creatinine, SGPT and/or SGOT, total bilirubin) at least weekly during induction and reinduction then every two weeks during consolidation.
- CBC, differential, platelet count, creatinine, and bilirubin prior to each consolidation course
- Bone marrow aspirate and/or biopsy starting day 33 of induction and reinduction (+/- 7 days) and every 2 weeks (+/- 7 days) thereafter until remission or non-response (Day 33 is listed instead of usual day 28 due to 5 days of decitabine treatment prior to chemotherapy). No bone marrow is necessary if non-response or progressive disease can

be diagnosed from peripheral blood evaluation, or, in patients with a WBC \leq 300/uL, if the bone marrow test is considered non-contributory by the Investigator. Cytogenetic studies need to be repeated only if abnormal prior to study. Further bone marrow tests as indicated by development of peripheral blood counts.

Marrow aspirates would be repeated every 2-3 cycles during consolidation phase

Optional procedures for the study

Samples will be collected for potential studies and will be stored in the laboratory of Dr. Guillermo Garcia-Manero (pager 713-404-0277) in the Department of Leukemia at MD Anderson Cancer Center. Samples will be collected as follows:

- Bone marrow aspirate: pretherapy (day 0) and on day 33 of first cycle.
- Peripheral blood (including serum): on days 0, 5, 10, 17, 24 and 33 of the first cycle.

All samples can be obtained +/- 5 days. Not all research samples may be collected at all time-points and omissions will not be considered deviations.

Samples could be used, but not limited, to analysis of cytokine profile, genetic and epigenetic lesions and molecular characterization of mechanism of action.

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 up to 4 doses of cytarabine (up to 2 g/m² each) for emergency use up to 24 hours prior to start of study therapy. Intrathecal chemotherapy is allowed for patients with CNS disease.

7. STUDY END POINTS

Phase I

Primary: To determine the MTD of clofarabine to be used in portion II of the study

Phase II

Primary: To determine the response rate of the DAC-CIA regimen

Secondary: A) To determine the toxicity of the combination regimen; B) To determine the DFS and OS rates

8. 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 CRp or CRi after 2 induction courses

9. CRITERIA FOR RESPONSE

Definitions:

Complete Response (CR): Disappearance of all clinical and/or radiologic evidence of disease.

Neutrophil count $\geq 1.0 \times 10^9/L$

Platelet count $\geq 100 \times 10^9/L$

Normal bone marrow differential ($\leq 5\%$ blasts)

No extra-medullary leukemia

Complete Remission without Platelet Recovery (CRp):

Peripheral blood and bone marrow results as for CR, but with platelet counts of $< 100 \times 10^9/L$.

Complete Remission without Incomplete Blood Count Recovery (CRi):

Peripheral blood and bone marrow results as for CR except for ANC $< 1.0 \times 10^9/L$ with or without platelet count $< 100 \times 10^9/L$.

Partial Remission (PR):

Blood count recovery as for CR, but with a decrease of at least 50% in the percentage of marrow blasts to $>5\%$ to 25% in the bone marrow aspirate.

Stable Disease (SD):

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.

10. REPORTING REQUIREMENTS

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

11. STATISTICAL CONSIDERATIONS

Phase I

First, phase I study is performed to assess the safety of different dosing schedules for clofarabine combined with fixed dosage of decitabine, idarubicin, and cytarabine. Two dose schedules are defined in table 1, and the starting dose schedule is dose level 1. A maximum of 18 AML patients will enroll in the phase I study.

Table 1: dose schedule

Dose level	Clofarabine 15 mg/m²/day IV daily
-1	Clofarabine daily for 3 days (days 6-8)
1	Clofarabine daily for 4 days (days 6-9)

Decitabine 20 mg/m² IV over approximately 1 hour daily for 5 days (days 1-5)

Idarubicin 10 mg/m² IV over approximately 30 minutes daily for 3 days (days 6-8)

Cytarabine 1 g/m² IV over approximately 2 hours daily for 5 days (days 6-10)

Dose Escalation Procedures

Starting with Dose level 1, the patient will be enrolled by cohort of 3. Once the DLT assessment for the 3 patients is completed, a sequential of another cohort of 3 patients will be enrolled. If at any time, we see more than 30% patients experiencing DLT, we will deescalate to dose level (-1). If no dose de-escalation occurs, with a total of 18 patients treated at dose level 1, dose level 1 will be considered as the MTD for the phase II part. If there is dose de-escalation, a cohort of 3 patients will be treated, Dose level -1 will be declared as MTD if there are ≤ 1 out of 6 patients experience DLT.

Phase II

Phase II part is a single arm study using the dosage schedule recommended from phase I. A maximum of 60 AML patients which includes 42 new patients and the 18 patients from phase I MTD level, and 20 ALL patients will be enrolled in the study. The trial will be continuously monitored regarding efficacy for each cohort, AML and ALL respectively. The toxicity will be jointly monitored for AML and ALL patients. The method of Thall, Simon, and Estey will be used to perform interim efficacy and safety monitoring.⁵³ The software Multc99.Version 2.1 was used to run the simulation.

Efficacy

The primary endpoint is the overall response which is defined as the best response (either CR, CRp, or CRi) within 56 days.

11.1 AML

For the AML patients, the historical data suggested the overall response rate to current standard treatment is 25%. The target response rate is 40%. The trial will be continuously monitored. The study will be stopped early if the data suggest that:

$$\Pr (\pi > 0.25|\text{data}) < 0.3$$

Here π is the overall response (OR) rate. That is, if at any time during the study we determine that there is a less than 30% chance that the average OR rate is greater than 25%, we will terminate the study. The OR rate is assumed to follow a non-informative prior of Beta (0.5, 1.5). The study will be stopped early if (The number of overall responses)/ (The number of patients evaluated) $\leq 1/8, 2/11, 3/15, 4/20, 5/24, 6/29, 7/33, 8/37, 9/42, 10/46, 11/50, 12/54, 13/59$.

Table 2: Operating characteristics for monitoring of overall response rate in AML patients

True Response Rate	Early Stopping Probability	Median Sample size (interquartile)
0.2	0.91	8 (8,20)
0.25	0.73	11 (8, 60)
0.3	0.51	54 (8, 60)
0.35	0.33	60 (15, 60)
0.4	0.19	60 (60, 60)

11.2. ALL

For the ALL patients, the historical data suggested the overall response rate to current standard treatment is 20%.The target response rate would be 40% after the treatment. The trial will be continuously monitored. The study will be stopped early if the data suggest that:

$$\Pr (\pi > 0.2|\text{data}) < 0.4$$

Here π is the overall response (OR) rate. That is, if at any time during the study we determine that there is a less than 40% chance that the average OR rate is greater than 20%, we will terminate the study. The OR rate is assumed to follow a non-informative prior of Beta (0.4, 1.6). The study will be stopped early if (The number of overall responses)/ (The number of patients evaluated) $\leq 1/8, 2/11, 3/17$.

Table 3: Operating characteristics for monitoring of overall response rate in ALL patients

True Response Rate	Early Stopping Probability	Median Sample size (interquartile)
0.15	0.85	8 (8,11)
0.2	0.7	11 (8, 20)
0.25	0.54	17 (8, 20)
0.3	0.38	20 (8,20)
0.35	0.26	20 (17, 20)
0.4	0.16	20 (20, 20)

Monitoring of non-hematological \geq grade 3 toxicities

With the concern of treatment related toxicity, the non-hematological toxicity (\geq grade 3) throughout all the cycles of treatment will also be closely monitored during the study for AML and ALL together.

Denote the probability of toxicity by P_E . We assume $P_E \sim \text{beta}(0.6, 1.4)$. Our stopping rule is given by the following probability statement: $\Pr(P_E > 0.3 \mid \text{data}) > 0.9$. That is, we will stop the trial if, at any time during the study, we determine that there is more than 90% chance that the toxicity rate is more than 30%. The study will be stopped early if (The number of non-hematological toxicities being grade 3 or higher)/ (The number of patients evaluated) \geq 7/13, 8/15, 9/18, 10/21, 11/23, 12/26, 13/29, 14/32, 15/35, 16/38, 17/41, 18/43, 19/46, 20/49, 21/52, 22/55, 23/58, 24/61, 25/64, 26/67, 27/70, 28/73, 29/76, 30/79. The operating characteristics are summarized in table 4.

Table 4: Operating characteristics for monitoring of non-hematological \geq grade 3 toxicities in AML or ALL patients

True Toxicity Rate	Early Stopping Probability	Median Sample size (interquantile)
0.25	0.15	80 (80, 80)
0.3	0.35	80 (27, 80)
0.35	0.63	42 (11, 80)
0.4	0.88	19 (7, 47)

Analysis method

Data analysis will be performed using SAS or S-plus, as appropriate. The proportion of patients having overall response, the mortality rate, and the proportion of patients having grade 3 or higher non-hematological toxicities will be estimated by the corresponding posterior mean and 90% posterior credible interval.

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