Phase I/II trial of cladribine, high-dose cytarabine, mitoxantrone, and G-CSF with dose-escalated mitoxantrone for relapsed/refractory acute myeloid leukemia and other high-grade myeloid neoplasms

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doi:10.3324/haematol.2018.204792

PATIENTS AND METHODS

Study population

Adults aged ≥18 years with a prior diagnosis of AML (acute promyelocytic leukemia excepted) or other myeloid neoplasms with ≥10% blasts in peripheral blood and/or bone marrow were eligible if they had relapsed or refractory disease (defined by standard morphologic criteria[1, 2]) and a treatment-related mortality (TRM) score of ≤6.9. This score, which can be computed via freely available online calculator (https://cstaging.fhcrc-research.org/TRM/), is composed of weighted information from 8 covariates (age, performance status, white blood cell [WBC] count, peripheral blood blast percentage, type of AML [de novo *vs*. secondary], platelet count, albumin, and creatinine) and corresponds to a ≤6.9% probability of death within 28 days ("TRM") of receipt of intensive chemotherapy for newly-diagnosed AML.[3] Patients had to have a left ventricular ejection fraction ≥45%, creatinine ≤2.0 mg/dL, and bilirubin ≤2.5 times the upper limit of normal, no uncontrolled infection, and an expected survival of >1 year absent AML. Prior autologous or allogeneic hematopoietic cell transplantation (HCT) was permitted provided any graft-versus-host disease was well controlled with stable use of immunosuppressive agents, as was prior therapy with mitoxantrone- or cladribine-based regimens. Cytogenetic risk was assessed according to the modified MRC/NCRI criteria.[4] Best treatment responses were defined according to standard criteria and measured after 1-2 cycles of therapy. Measurable ('minimal') residual disease (MRD) was assessed by multiparametric flow cytometry, with any level of MRD considered positive (MRD^{pos}).[5-7] Relapse after study treatment was defined by standard morphologic criteria[1, 2] or emergence of MRD if resulting in a therapeutic intervention. The protocol was approved by the Fred Hutchinson Cancer Research Center (Fred Hutch) Institutional Review Board (IRB), and patients gave written informed consent in accordance with the Declaration of Helsinki.

Treatment plan

Because the safety of CLAG-M with mitoxantrone at 10 mg/m^2 on days 1-3 is well established,[8] patients were assigned to 12, 14, 16, or 18 mg/m^2 of intravenous (IV) mitoxantrone on days 1-3 in phase 1. G-CSF was given subcutaneously at 300 or 480 µg (for weight <76 kg *vs*. ≥76 kg; days 0-5), cladribine IV at 5 mg/m^2 (days 1-5), and cytarabine IV at 2 g/m^2 (days 1-5). The first 2 doses of G-CSF could be omitted if the total WBC count was >20,000/µL. In phase 2, patients received mitoxantrone at the MTD identified in phase 1. A second identical course of CLAG-M was given for patients who did not achieve complete remission (CR) or CR with incomplete hematologic recovery (CRi) with cycle 1. Patients in CR/CRi after 1-2 cycles could receive up to

4 cycles of GCLA (mitoxantrone omitted). Patients were taken off study for failure to achieve CR/CRi after 2 cycles of therapy, alternative consolidation including HCT, excess toxicity including persistent aplasia without evidence of leukemia after day 45 of treatment, or relapse. Toxicities were evaluated based on the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.03 (http://ctep.cancer.gov).

Comparisons with other intensive re-induction chemotherapy regimens

Data were obtained from patients treated at our institution with 1) CLAG-M at the standard mitoxantrone dose; 2) GCLAC (G-CSF 5 µg/kg SC from day 0 until neutrophil recovery; clofarabine 15-25 mg/m^2 IV on days 1-5; cytarabine 2 g/m^2 IV on days 1-5); and 3) decitabine-primed MEC (decitabine 20 mg/m^2 for 7 or 10 days, 5-day break, then standard-dose MEC [mitoxantrone 8 mg/m^2 IV on days 1-5; etoposide 100 mg/m^2 IV on days 1-5; cytarabine 1 g/m^2 IV on days 1-5]). Patients received GCLAC and decitabine-primed MEC either as part of two phase 1/2 studies (NCT00602225[9, 10] and NCT01729845[11], respectively) or off-protocol. Previous analyses found no differences in outcomes of similar patients treated with the same regimen on- vs. off-protocol.[12] Covariates collected included age, sex, cytogenetic risk category, primary vs. secondary disease, prior HCT, duration of first CR, performance status, TRM score, WBC and platelet count, peripheral blood blast percentage, *FLT3* and *NPM1* mutational status, and whether or not treatment occurred as part of a clinical trial. The Fred Hutch IRB approved this retrospective analysis.

Statistical considerations

In phase 1, cohorts of 6 patients were assigned to increasing doses of mitoxantrone. Dose-limiting toxicity (DLT) was defined as: 1) any grade 3 non-hematologic toxicity, other than febrile neutropenia or infection, lasting >48 hours that resulted in a >7-day delay of subsequent treatment; 2) any grade ≥4 non-hematologic toxicity, other than febrile neutropenia or infection or constitutional symptoms if recovery to grade ≤2 within 14 days. Cumulative toxicities were assessed after every treatment cycle. The maximum tolerated dose (MTD) was assumed to be the RP2D and was defined as the highest dose studied in which the incidence of DLTs was <33%. If ≤2/6 (33%) on one dose level had toxicity, 6 additional patients could be enrolled for further evaluation of that dose level. For phase 2, we considered CLAG-M at the MTD of no further interest if the CR rate was ≤15% (null hypothesis)[13] while a CR rate ≥30% would spur further investigation (alternative hypothesis). A Simon Optimal 2-stage design[14] was used, with 80% power and a 1-sided alpha of 7%, thus calling for enrollment of 20 patients in each the first

and second stages, with the study deemed futile if CR was obtained in <3/21 or <10/40 patients. With this design, the probability the study would be stopped after the first stage of accrual is 41% if the true response rate is 15%; if the true response rate is 30%, the probability the study would be stopped after the first stage of accrual is 4%. Overall survival (OS) and relapse-free survival (RFS) were estimated using the Kaplan-Meier method and compared using log-rank and Cox regression models. Multivariable logistic and Cox regression models were used to compare outcomes between dose levels of mitoxantrone as well as to compare outcomes following CLAG-M with escalated mitoxantrone doses to other treatment regimens. Fisher's exact test was used to compare 4-week mortality rates. Data cut-off date for analysis was May 11, 2018.

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SUPPLEMENTAL TABLE 1. Patient characteristics, phase 1

Parameter	n= 26
Median age (range), years	57 (37-77)
Male gender, n (%)	14 (54%)
Disease-type	
AML	
With recurrent genetic abnormalities	1 (4%)
With mutated NPM1	4 (15%)
With myelodysplasia-related changes	5 (23%)
Treatment-related AML	2 (7%)
AML from antecedent hematologic disorder	5 (23%)
AML, not otherwise specified	8 (4%)
MDS-EB2	1 (4%)
Secondary disease*	7 (27%)
Disease status, n (%)	
Primary refractory	5 (19%)
Relapse	21 (81%)
Median CR1 duration (range), months	8 (2-120)
Prior HCT	9 (35%)
Median number of prior therapies (range)	2 (1-5)
Median TRM score (range)	1.73 (0.29-3.92)
Performance status, n. (%)	
0	15 (58%)
1	11 (42%)
Cytogenetic risk, n (%)	
Intermediate	15 (58%)
Adverse	11 (42%)
Mutational status, n (%)	
FLT3-ITD	
Wild-type	14 (54%)
Mutated	4 (15%)
Unknown	8 (31%)
NPM1	
Wild-type	13 (50%)
Mutated	4 (15%)
Unknown	9 (35%)
Laboratory findings at baseline, median (range)	
WBC (x 10^9L)	3.5 (0.2-51.4)
Peripheral blood blasts (%)	5 (0-84)
Hemoglobin (g/dL)	9.9 (7.7-14.7)
Platelets (x 10^9L)	80 (8-283)
Creatinine (mg/dL)	0.9 (0.6-1.6)
Total bilirubin (mg/dL)	0.6 (0.3-1.4)

Abbreviations: CR1, first complete remission; HCT, allogeneic stem cell transplant; TRM, treatment-related mortality score; WBC, white blood cell count *Defined either as AML transformed from antecedent hematologic disorder, or AML/MDS in a patient who had previously received cytotoxic therapy.

*Defined either as AML transformed from antecedent hematologic disorder, or AML/MDS in a patient who had previously received cytotoxic therapy

SUPPLEMENTAL TABLE 2. Dose escalation scheme, best responses, and dose-limiting toxicities during phase 1, n=26

Dose Level	**G-CSF** (D0 to D5)	**Cladribine** (D1 to D5)	**Cytarabine** (D1 to D5)	**Mitoxantrone** (D1 to D3)	**Patients** (n)	**Best response***	**Dose-limiting toxicities**
1	300 or 480 µg	5 mg/m^2	2 g/m^2	12 mg/m^2	10	4 CR (1 MRD^{neg}), 1 CRi (MRD$^{neg)}$, 5 RD	Nausea
2	300 or 480 µg	5 mg/m^2	2 g/m^2	14 mg/m^2	6	1 CR (MRD^{neg}), 2 CRi (2 MRD$^{neg)}$, 2 MLFS, 1 NE	None
3	300 or 480 µg	5 mg/m^2	2 g/m^2	16 mg/m^2	6	2 CR (1 MRD^{neg}), 1 CRi (MRD$^{pos)}$, 2 RD, 1 DI	None
4	300 or 480 µg	5 mg/m^2	2 g/m^2	18 mg/m^2	4	2 CR (1 MRD^{neg}), 1 RD, 1 DI	Encephalopathy, cardiogenic shock

*The response for 1 patient treated at dose level 2 could not be assessed due to refusal to undergo bone marrow staging

Abbreviations: CR, complete remission; MRD, measurable residual disease; CRi, CR with incomplete hematologic recovery; RD, resistant disease, MLFS, morphologic leukemia free state; NE, not evaluable DI: death from indeterminate cause.

SUPPLEMENTAL TABLE 3. Safety and tolerability at the RP2D level

Parameter, n= 40	Grade 3-4, n (% of cycles)	Grade 5, n (% of cycles)
Fever, infection		
Bloodstream infection	29 (58%)	0
Catheter-related infection	2 (4%)	0
Colitis, C. difficile	2 (4%)	0
Disseminated fungal infection	1 (2%)	1 (2%)
Fungal skin infection	1 (2%)	0
Lung infection	2 (4%)	1 (2%)
Lung infection, fungal	8 (16%)	0
Neutropenic fever	48 (96%)	0
Oral infection	1 (2%)	0
Sepsis	3 (6%)	1 (2%)
Sinusitis	2 (4%)	0
Soft-tissue infection	11 (22%)	0
Upper respiratory tract infection	1 (2%)	0
Cardiac		
Atrial tachycardia	1 (2%)	0
Cardiomyopathy	3 (6%)	0
Edema	1 (2%)	0
Hypotension	5 (10%)	0
Myo/Pericarditis	1 (2%)	0
Gastrointestinal		
Diarrhea	2 (4%)	0
Enteritis	1 (2%)	0
Esophagitis	2 (4%)	0
Gastrointestinal hemorrhage	1 (2%)	0
Ileus	1 (2%)	0
Mucositis	3 (6%)	0
Nausea	1 (2%)	0
General		
Fever	1 (2%)	0
Investigations		
Acute kidney injury	2 (4%)	0
Alanine aminotransferase increase	2 (4%)	0
Alkaline phosphatase increase	1 (2%)	0
Aspartate aminotransferase increase	2 (4%)	0
Bilirubin increase	2 (4%)	0
Cardiac troponin	1 (2%)	0
Metabolism and nutritional		
Hypokalemia	1 (2%)	0
Hyponatremia	1 (2%)	0
Hypophosphatemia	1 (2%)	0
Tumor lysis	6 (12%)	0
Nervous system disorders		
Aphasia	1 (2%)	0
Headache	2 (4%)	0
Seizure	1 (2%)	0
Syncope	1 (2%)	0

Respiratory		
Hypoxia	8 (16%)	0
Pulmonary edema	1 (2%)	0
Respiratory failure	2 (4%)	0
Vascular disorders		
Catheter-associated thrombosis	1 (2%)	0
Other		
Anxiety	1 (2%)	0
Bone pain	1 (2%)	0
Fall	1 (2%)	0
Myotendinitis	1 (2%)	0
Ocular myositis	1 (2%)	0
Rash	5 (10%)	0

Table summarizing grade 3-5 non-hematologic effects considered as definitively, probably, or possibly related to study treatment by the investigator that were experienced during study treatment by the 40 patients treated at the RP2D on trial over 50 cycles of therapy.

SUPPLEMENTAL TABLE 4. Comparison of baseline characteristics and outcomes of patients with primary refractory disease vs. those with relapsed disease, treated at the RP2D

Parameter	Primary Refractory Disease n=20*	Relapsed Disease n=20
Median age (range), years	65 (39-70)	50 (33-77)
Male gender, n (%)	11 (55%)	13 (65%)
Performance status, n (%) 0-1 2-3	 20 (100%) 0	 18 (90%) 2 (10%)
Median TRM score (range)	3.34 (0.42-6.39)	1.77 (0.25-6.26)
Median duration of CR1 (range), months	0	11.5 (1-86)
Median number prior therapies, n (range)	1 (1-3)	2 (1-6)
Prior HCT	0	7 (35%)
Secondary disease**	8 (40%)	2 (10%)
Cytogenetic risk, n (%) Intermediate Adverse	 11 (55%) 9 (45%)	 14 (70%) 6 (30%)
Overall response, n CR MRD^{neg} CR CR/CRi	 6 (30%) 5 (25%) 12 (60%)	 5 (25%) 4 (20%) 12 (60%)
Subsequent HCT	11 (55%)	11 (55%)
Number of grade ≥3 adverse events per patient, cycle 1, median (range)	3 (0-8)	3 (0-13)
4-week mortality	1 (5%)	1 (5%)
8-week mortality	1 (5%)	1 (5%)

*10 primary refractory patients had received only prior hypomethylating agents (either azacitidine or decitabine alone or sequential administration of both agents).

Abbreviations: RP2D, recommended phase 2 dose; TRM, treatment related mortality score; CR1, first complete remission; HCT, allogeneic hematopoietic cell transplantation; MRD, measurable residual disease; CRi, CR with incomplete hematologic recovery.

**Defined either as AML transformed from antecedent hematologic disorder, or AML/MDS in a patient who had previously received cytotoxic therapy

SUPPLEMENTAL TABLE 5. Comparison of characteristics and treatment outcomes of younger vs. older study participants treated at the RP2D

Patient Characteristic	Age<65 (n=22)	Age ≥65 (n=18)
Disease		
AML	19 (86%)	15 (83%)
MDS-EB-2	3 (14%)	3 (17%)
Disease status, n (%)		
Primary refractory	8 (36%)	12 (67%)
Relapse	14 (64%)	6 (33%)
CR1 duration median (range), months	14 (1-86)	8 (2-54)
Prior HCT	7 (32%)	0
Number of prior therapies median (range)	2 (1-6)	2 (1-4)
Secondary disease*	4 (18%)	6 (33%)
Median TRM score (range)	1.6 (0.2-5.4)	3.7 (1.0-6.4)
Cytogenetic risk, n (%)**		
Intermediate	11 (50%)	14 (78%)
Adverse	11 (50%)	4 (22%)
Response		
CR, n (%)	7 (32%)	4 (22%)
MRD^{neg} CR, n (%)	6 (27%)	3 (17%)
CRi, n (%)	7 (32%)	6 (33%)
CR/CRi, n (%)	14 (64%)	10 (56%)
PR/MLFS	0	1 (6%)
Resistant disease	7 (32%)	4 (22%)
Death from indeterminate cause	1 (5%)	1 (6%)
Unable to assess	0	2 (11%)
Subsequent allogeneic HCT	12 (55%)	10 (56%)
1-year overall survival	52%	33%
1-year relapse-free survival	54%	40%
4-week mortality	1 (5%)	1 (6%)
8-week mortality	1 (5%)	1 (6%)

*Defined either as AML transformed from antecedent hematologic disorder, or AML/MDS in a patient who had previously received cytotoxic therapy

Abbreviations: RP2D, recommended phase 2 dose; CR, complete remission; MRD, measurable residual disease; CRi, CR with incomplete hematologic recovery; PR, partial remission; MLFS, morphologic leukemia free state; TRM, death within 28 days of therapy initiation.

SUPPLEMENTAL TABLE 6. Comparison of baseline study characteristics between standard-dose GLCAM (mitoxantrone 10 mg/m^2) and dose-escalated CLAG-M (mitoxantrone 16 mg/m^2)

Regimen	CLAG-M with Mito 10 mg/m^2 (n=30)	CLAG-M with Mito 16 mg/m^2 (n=51)	P-value
Median age (range), years	54 (19-76)	59 (33-77)	0.14
Male gender, n (%)	17 (57%)	29 (57%)	1.00
Performance status, n. (%)			0.19
0-1	26 (87%)	48 (96%)	
2-3	4 (13%)	2 (4%)	
Median TRM score (range)	3.20 (0.19-6.90)	2.41 (0.25-6.39)	0.10
Median duration of CR1 (range), months	3 (0-81)	2 (0-86)	0.57
Prior HCT	10 (33%)	8 (16%)	0.10
Secondary disease*	6 (20%)	13 (25%)	0.79
Cytogenetic risk, n (%)			0.81
Favorable/intermediate	20 (69%)	33 (65%)	
Adverse	9 (31%)	18 (35%)	
Mutational status, n (%)			
FLT3-ITD			0.39
Wild-type	17 (59%)	28 (57%)	
Mutated	5 (17%)	4 (8%)	
Unknown	7 (24%)	17 (35%)	
NPM1			0.40
Wild-type	15 (52%)	18 (37%)	
Mutated	3 (10%)	9 (18%)	
Unknown	11 (38%)	22 (45%)	
Laboratory findings at baseline, median (range)			
WBC (x 10^9L)	2 (0-97)	3 (0-48)	0.36
Platelets (x 10^9L)	36 (6-389)	67 (6-328)	0.02
Overall response, n			
CR	10 (33%)	13 (25%)	0.46
MRD^{neg} CR	7 (23%)	11 (22%)	1.00
CR/CRi	14 (47%)	29 (57%)	0.49
Subsequent HCT	11 (38%)	30 (59%)	0.10
Median overall survival, months	7	16	0.002^
1-year overall survival	21%	53%	
4-week mortality	1 (3%)	2 (4%)	1.00

Abbreviations: Mito, mitoxantrone; CR1, first complete remission; HCT, allogeneic hematopoietic cell transplantation; WBC, white blood cell count; MRD, measurable residual disease; CRi, CR with incomplete hematologic recovery.

*Defined either as AML transformed from antecedent hematologic disorder, or AML/MDS in a patient who had previously received cytotoxic therapy

^Log-rank p-value for OS comparisons.

SUPPLEMENTAL TABLE 7: Comparison of response rates and survival between CLAG-M with mitoxantrone at 10 mg/m^2 and 16 mg/m^2, TRM score ≤ 6.9

	CR/CRi OR (95% CI), p-value	CR +/- MRD OR (95% CI), p-value	MRD^{neg} CR OR (95% CI), p-value	OS OR (95% CI), p-value	RFS OR (95% CI), p-value
CLAG-M 10 (ref= CLAG-M 16)	0.55 (0.20-1.48), 0.24	1.19 (0.40-3.56), 0.75	0.74 (0.22-2.55), 0.63	2.65 (1.44-4.89), 0.002	1.51 (0.62-3.69), 0.37
Age (years)	1.00 (0.96-1.04), 0.92	0.98 (0.94-1.02), 0.45	0.97 (0.93-1.02), 0.24	1.02 (0.99-1.04), 0.15	1.03 (0.98-1.07), 0.24
Fav/int cytogenetic risk (ref= adverse risk)	2.21 (0.79-6.13), 0.13	1.64 (0.50-5.31), 0.41	3.43 (0.81-14.54), 0.10	0.60 (0.33-1.11), 0.11	0.84 (0.33-2.12), 0.71
CR1 duration (months)	0.98 (0.95-1.02), 0.33	0.96 (0.90-1.02), 0.15	0.97 (0.91-1.03), 0.25	1.01 (0.99-1.02), 0.51	1.02 (0.98-1.05), 0.40
Prior HCT (ref= no prior HCT)	1.37 (0.33-5.75), 0.67	1.02 (0.21-5.04), 0.98	1.11 (0.19-6.52), 0.91	1.33 (0.61-2.91), 0.48	1.01 (0.33-3.13), 0.99

Abbreviations: TRM, treatment-related mortality; CR, complete remission; CRi, CR with incomplete hematologic recovery; MRD, measurable residual disease, OS, overall survival; RFS, relapse free survival; OR, odds ratio; CI, confidence interval; Ref, reference; Fav, favorable; Int, intermediate; HCT, allogeneic hematopoietic cell transplantation.

SUPPLEMENTAL TABLE 8: Comparison of response rates and survival between CLAG-M with mitoxantrone at 10 mg/m^2 and 16 mg/m^2, all TRM scores

	CR/CRi OR (95% CI), p-value	CR +/- MRD OR (95% CI), p-value	MRD^{neg} CR OR (95% CI), p-value	OS OR (95% CI), p-value	RFS OR (95% CI), p-value
CLAG-M 10 (ref= CLAG-M 16)	0.55 (0.22-1.39), 0.20	2.17 (0.70-6.66), 0.18	1.28 (0.37-4.35), 0.69	2.04 (1.16-3.57), 0.01	1.03 (0.43-2.44), 0.95
Age (years)	1.02 (0.98-1.06), 0.33	1.00 (0.96-1.05), 0.90	0.99 (0.95-1.04), 0.70	1.01 (0.99-1.04), 0.28	1.03 (0.98-1.07), 0.24
Fav/int Cytogenetic risk (ref= adverse risk)	1.68 (0.67-4.20), 0.26	1.20 (0.41-3.47), 0.74	2.73 (0.74-10.08), 0.13	0.71 (0.41-1.21), 0.20	0.71 (0.30-1.67), 0.43
CR1 duration (months)	0.98 (0.95-1.01), 0.30	0.95 (0.89-1.01), 0.11	0.96 (0.90-1.02), 0.18	1.01 (0.99-1.02), 0.44	1.02 (0.99-1.05), 0.18
Prior HCT (ref= no prior HCT)	1.46 (0.42-5.07), 0.55	0.89 (0.21-3.76), 0.87	1.15 (0.24-5.54), 0.86	1.23 (0.65-2.35), 0.53	0.97 (0.38-2.51), 0.95
TRM score	0.90 (0.79-1.03), 0.14	0.78 (0.63-0.98), 0.04	0.78 (0.60-1.01), 0.06	1.07 (1.01, 1.12), 0.02	1.11 (0.96-1.29), 0.16

Abbreviations: TRM, treatment-related mortality; CR, complete remission; CRi, CR with incomplete hematologic recovery; MRD, measurable residual disease, OS, overall survival; RFS, relapse free survival; OR, odds ratio; CI, confidence interval; Ref, reference; Fav, favorable; Int, intermediate; HCT, allogeneic hematopoietic cell transplantation.

SUPPLEMENTAL TABLE 9. Comparison of baseline study characteristics across salvage regimens

Regimen	CLAG-M RP2D (n=40)	d/MEC (n=36)	G-CLAC (n=56)	P-value
Median age (range), years	63 (33-77)	55 (19-73)	50 (19-66)	<0.001
Male gender, n (%)	24 (60%)	17 (47%)	37 (66%)	0.22
Performance status, n. (%)				
0-1	38 (95%)	35 (97%)	49 (88%)	0.21
2-3	2 (5%)	1 (3%)	7 (12%)	
Median TRM score (range)	2.10 (0.25-6.39)	2.42 (0.07-6.74)	3.42 (0.16-6.90)	0.15
Median duration of CR1 (range), months	0.5 (0-86)	3.0 (0-18)	0.5 (0-60)	0.55
Prior HCT	7 (18%)	11 (31%)	9 (16%)	0.22
Secondary disease*	10 (25%)	5 (14%)	12 (21%)	0.47
Cytogenetic risk, n (%)				0.68
Favorable/intermediate	25 (62%)	20 (56%)	35 (65%)	
Adverse	15 (38%)	16 (44%)	19 (35%)	
Mutational status, n (%)				
FLT3-ITD				0.04
Wild-type	22 (55%)	20 (56%)	20 (36%)	
Mutated	1 (2%)	2 (6%)	11 (20%)	
Unknown	17 (42%)	14 (39%)	25 (45%)	
NPM1				0.60
Wild-type	14 (35%)	17 (47%)	18 (32%)	
Mutated	6 (15%)	5 (14%)	7 (12%)	
Unknown	20 (50%)	14 (39%)	31 (55%)	
Laboratory findings at baseline, median (range)				
WBC (x 10^9L)	3 (0-48)	2 (0-59)	5 (0-78)	0.07
Platelets (x 10^9L)	68 (6-328)	49 (4-457)	63 (11-437)	0.09
Overall response, n				
CR	11 (28%)	2 (22%)	26 (46%)	0.03
MRD^{neg} CR	9 (22%)	7 (19%)	15 (27%)	0.73
CR/CRi	24 (60%)	13 (36%)	28 (50%)	0.12
Subsequent HCT	22 (55%)	10 (29%)	25 (45%)	0.05
Median overall survival, months	11	5	7	0.02^
1-year overall survival	44%	21%	29%	
4-week mortality	2 (5%)	3 (8%)	0	0.08

Abbreviations: TRM, treatment-related mortality score; CR1, first complete remission; Mos, months; HCT, allogeneic stem cell transplant; WBC, white blood cell count; MRD, measurable residual disease; CRi, CR with incomplete hematologic recovery.

*Defined either as AML transformed from antecedent hematologic disorder, or AML/MDS in a patient who had previously received cytotoxic therapy

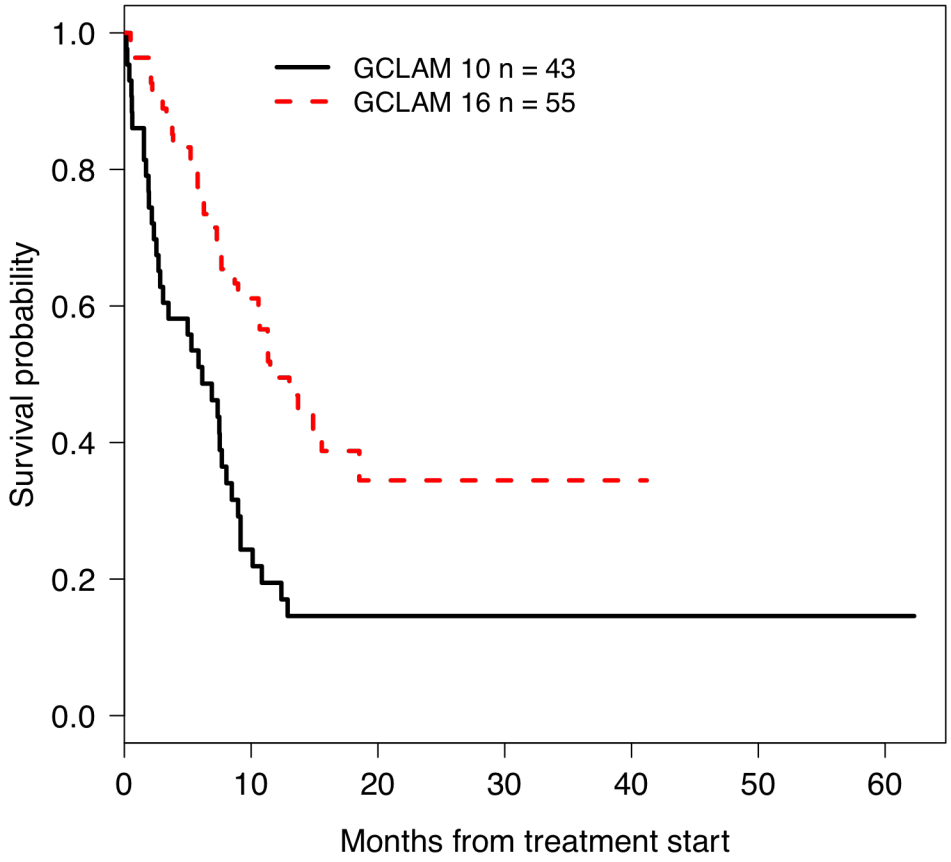
^Log-rank p-value for OS comparisons

SUPPLEMENTAL TABLE 10: Comparison of response rates and survival between CLAG-M with mitoxantrone 16 mg/m^2, decitabine-MEC and GCLAC

	CR/CRi OR (95% CI), p-value	CR +/- MRD OR (95% CI), p-value	MRD^{neg} CR OR (95% CI), p-value	OS OR (95% CI), p-value
DMEC (ref= CLAG-M 16)	0.35 (0.13-0.98), 0.05	0.59 (0.19-1.86), 0.37	0.72 (0.21-2.47), 0.61	2.02 (1.15-3.53), 0.01
GCLAC (ref= CLAG-M 16)	0.55 (0.21-1.43), 0.22	1.70 (0.63-4.56), 0.29	0.97 (0.32-2.95), 0.98	1.46 (0.86-2.49), 0.16
Age (years)	0.99 (0.96-1.02), 0.60	0.99 (0.96-1.02), 0.37	0.99 (0.96-1.03), 0.65	1.00 (0.99-1.02), 0.86
Fav/int cytogenetic risk (ref= adverse risk)	2.27 (1.07-4.80), 0.03	1.72 (0.77-3.84), 0.19	3.14 (1.17-8.46), 0.02	0.54 (0.36-0.81), 0.003
CR1 duration (months)	0.99 (0.96-1.02), 0.61	0.98 (0.93-1.02), 0.25	0.98 (0.94-1.03), 0.46	0.99 (0.98-1.01), 0.55
Prior HCT (ref= no prior HCT)	0.68 (0.24-1.89), 0.46	1.10 (0.37-3.25), 0.86	1.29 (0.40-4.18), 0.67	1.29 (0.73-2.28), 0.38

Abbreviations: TRM, treatment-related mortality; CR, complete remission; CRi, CR with incomplete hematologic recovery; MRD, measurable residual disease, OS, overall survival; RFS, relapse free survival; OR, odds ratio; CI, confidence interval; Ref, reference; Fav, favorable; Int, intermediate; HCT, allogeneic hematopoietic cell transplantation

SUPPLEMENTAL FIGURE 1



Comparison of OS of CLAG-M 10 vs CLAG-M 16, all TRM scores. Kaplan-Meier estimates of overall survival of patients who received CLAG-M with mitoxantrone at 10 mg/m^2 compared to patients who received CLAG-M with mitoxantrone at 16 mg/m^2, regardless of baseline TRM score.