



Published in final edited form as:

Leuk Lymphoma. 2010 January ; 51(1): 73–78. doi:10.3109/10428190903318329.

Report of a phase 1/2 study of a combination of azacitidine and cytarabine in acute myelogenous leukemia and high-risk myelodysplastic syndromes

GAUTAM BORTHAKUR¹, XUELIN HUANG², HAGOP KANTARJIAN¹, STEFAN FADERL¹, FARHAD RAVANDI¹, ALESSANDRA FERRAJOLI¹, RITVA TORMA¹, GAIL MORRIS¹, DONALD BERRY², and JEAN-PIERRE ISSA¹

¹ Department of Leukemia, University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

² Division of Quantitative Science, University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

Abstract

Cytarabine resistance characterizes relapsed and refractory acute myelogenous leukemia (AML). Restoration of cytarabine sensitivity can potentially improve treatment outcome in this setting. Acquired hypermethylation of gene promoters and associated silencing of gene expression has been implicated in chemo resistance, and drug-induced hypomethylation can improve sensitivity to cytarabine *in vitro*. We conducted an adaptively randomized study of a combination of azacitidine, a hypomethylating agent, and cytarabine in 34 patients with AML. The combination administered in a concomitant fashion is safe at full doses of azacitidine and cytarabine, without unexpected toxicities. However, in this advanced AML population, it was difficult to deliver more than one cycle of therapy, and minimal anti-leukemia activity was seen in patients with relapsed/refractory disease. Complete remission was achieved in 2 of 6 minimally pre-treated patients. We conclude that the combination of azacitidine and cytarabine is feasible but has limited activity in relapsed/refractory AML.

Keywords

Acute myelogenous leukemia; azacitidine; cytarabine

Introduction

Epigenetic silencing of tumor suppressor genes has been implicated as a mechanism of resistance to chemotherapy but target genes are not well defined. DNA methylation is one such mediator of epigenetic silencing. Drug-induced increased methylation is well documented, and has been suggested to be a part of acquired drug resistance [1,2]. In acute myelogenous leukemia (AML), DNA methylation increases at relapse post-chemotherapy-induced complete remission (CR) [3], and methylation at remission predicts for a high rate of disease relapse [4]. Drugs that reverse DNA methylation are now in routine use in myeloid leukemias [5], and it has been hypothesized that hypomethylation could reverse drug resistance in AML.

Azacitidine (5-AC) is a ring analog of the naturally occurring pyrimidine nucleoside, cytidine with replacement of carbon by nitrogen in position 5 of the cytidine heterocyclic ring. The initial step in activation of 5-AC intracellularly is the conversion to 5-azacytidine monophosphate (5-ACMP) by uridine-cytidine kinase [6]. 5-ACMP is further phosphorylated to 5-AC di- and triphosphate by CMP-UMP-dCMP kinases and nucleoside diphosphate kinases, respectively. 5-AC triphosphate can potentially be incorporated into RNA [7,8]. 5-AC diphosphate on the other hand can also be reduced to 5-azadeoxycytidine diphosphate (5-AdCDP) by ribo-nucleotide reductase. 5-AdCDP in turn can be phosphorylated by nucleoside diphosphate kinase to 5-azadeoxycytidine triphosphate (5-AdCTP) and can be incorporated into DNA [9,10]. Incorporation into RNA can inhibit the processing of ribosomal RNA from higher-molecular-weight species, disassembly of polyribosomes, and markedly inhibit protein synthesis [11]. At millimolar concentrations of 5-AC, incorporation into DNA could inhibit DNA synthesis and induce cell cycle arrest [12]. At lower dose, 5-AC (2–10 μ M) inhibits DNA methylation through stoichiometric binding with DNA-methyltransferase (DNMT) after incorporation to DNA [13–15]. Randomized phase III trials have established the activity of 5-AC in myelodysplastic syndrome (MDS) with improvement in cytopenias, decrease in progression to AML [16,17] and more recently improvement in survival compared with conventional care regimens [18].

Cytarabine is a nucleoside analog of deoxycytidine and is the most potent and most widely used antileukemic agent against AML. Mechanisms of resistance to cytarabine include but are not limited to reduced influx of by the hENT1 transporter, reduced phosphorylation by deoxycytidine kinase (dCK), and increased degradation by cytoplasmic 5'-nucleotidase (5NT) and/or cytidine deaminase (CDD) [19–23]. *In vitro*, hypomethylation induction by 5-aza-2'-deoxycytidine (decitabine) sensitizes to cell killing by cytarabine, and the combination is synergistic in myeloid leukemia cell lines [24]. However, cytarabine and decitabine have similar intracellular metabolic pathways and shared mechanisms of resistance [25]. Study of resistance to decitabine in leukemia cells indicated decreased incorporation of decitabine in DNA as the major mechanism and results from reduced dCK activity, increased transporters and deamination by CDD, reminiscent of resistance to cytarabine. Despite the fact that decitabine causes DNA hypomethylation at low doses, resistance to decitabine does not appear to be related to the expression of DNMT.

Based on these data, we hypothesized that reversal of DNA methylation in leukemia cells can potentially modify sensitivity to cytarabine *in vivo*. Because of shared mechanisms of resistance between decitabine and cytarabine, we chose to test this hypothesis by combining 5-AC with cytarabine in patients with refractory or relapsed AML or high risk MDS. This study used a novel adaptive clinical trial design [26] that seamlessly transitions from phase I to a randomized phase II component, allowing simultaneous assessment of toxicity and (preliminary) efficacy across a range of doses.

Materials and methods

Eligibility

Patients with refractory or relapsed (first CR <6 months or \geq 2nd relapse) AML and previously treated high-risk MDS were eligible. Eligibility criteria included (i) Eastern Co-operative Oncology Group performance status \leq 2; (ii) age 18 years or older; (iii) adequate hepatic function (serum bilirubin <2 mg/dL, aspartate aminotransferase (AST), alanine aminotransferase (ALT) \leq 2.5 \times upper limit of normal, creatinine <2 mg/dL); (iv) no chemotherapy except hydroxyurea within 4 weeks of study drug treatment. Previously untreated patients with AML or high-risk MDS were considered for the phase II portion. All patients gave informed consent according to federal and institutional guidelines.

Study design

Patients were assigned to one of four treatment groups for induction therapy (Table I).

In the first phase of the study, three patients were assigned to group 1. After confirming safety, enrollment in groups 2 and 3 was opened, and patients were adaptively randomized to three groups. Group 4 was included in the randomization after groups 2 and 3 were deemed safe. Adaptive randomization was based on the responses already observed in each group. The primary end points of the study were dose limiting toxicities (DLT) and clinically relevant responses including CR, CR with incomplete platelet recovery (CRp), partial remission (PR) as defined by Cheson *et al.* [27]. Responses in MDS were assessed according to the International Working Group (IWG) criteria [28]. Initial marrow aspiration/biopsy to assess response to induction therapy was done in week 3 and repeated in another week if not in remission. Subsequent marrow evaluations were done as clinically indicated. Toxicity was based on NCI Common Toxicity Criteria Version 3.0. DLT was defined as \geq Grade 3 non-hematological toxicity that could not be explained by intercurrent conditions such as infections. Hematological toxicity was not considered DLT unless there was myelosuppression lasting 8 weeks or more in the absence of evidence of active disease by peripheral blood or bone marrow examination.

Treatment plan

Starting drug dosages are described in Table I. Dose modifications of cytarabine or 5-AC or both were allowed based on toxicities in previous cycles. Prophylactic (oral) antibiotics such as levofloxacin and oral antifungals such as fluconazole were recommended for all patients. Granulocyte colony stimulating factor (G-CSF) use was allowed in patients with neutropenic fever according to ASCO guidelines (www.asco.org; guidelines@asco.org).

Patients were to receive two cycles of the assigned regimen. The second cycle was given upon recovery of peripheral blood counts (4–8 weeks after first cycle) in the absence of disease progression or intercurrent illnesses. Patients with evidence of response after two cycles were to receive maintenance therapy every 4–8 weeks (upon recovery of counts) with 5-AC for days 1–5 and cytarabine days 1–2 (for ≥ 65 years of age) or days 1–3 (for ≥ 65 years of age) at assigned dose levels for induction therapy. In the absence of treatment delays due to adverse events and with continued response, treatment could continue until 1 year in CR.

All patients who received therapy on study were considered evaluable for toxicity. Dose limiting toxicity was defined as Grade 3 or higher non-hematological toxicity by revised National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0) (Exception: alopecia, or nausea and vomiting in the absence of appropriate antiemetics) that cannot be explained by intercurrent conditions (e.g. infections). Hematologic toxicity was not to be considered dose limiting unless there was evidence of myelosuppression lasting 8 weeks or more in the absence of evidence of active disease by peripheral blood or bone marrow examination.

The historical CR rate for patients with relapsed/refractory AML as defined in this study is as low as 5%. The target response rate for the experimental combination was 20%. Response and toxicity were to be evaluated at 6 weeks after treatment. We used common AML response criteria [27].

Results

Patient characteristics

Thirty-four patients (all with AML) were enrolled; 6 in each of groups 1 and 2 and 11 in each of groups 3 and 4. Patient's characteristics are summarized in Table II. Thirty patients had relapsed/refractory AML including 7 patients with an antecedent hematological disorder (AHD) (preceding MDS or myeloproliferative disorder). Two patients with untreated AML were enrolled after discussion with the Principal Investigator as their outcome expectations were poor (one with complex cytogenetics, renal dysfunction being ineligible for front-line studies and another with AML developing from myelofibrosis and long exposure to hydroxyurea) and one patient received only one cycle of 5-AC prior to going on study. Another patient with prior AML had been in CR for over a year before enrolling in study with relapsed disease with complex cytogenetics. The median number of prior therapies was 2 (range 0–6). Excluding the patient with only one cycle of prior 5-AC, 9 patients (27%) had prior exposure to hypomethylating agents. Twenty-one patients (62%) had received high-dose cytarabine (HDAC) based therapies. Six patients (19%) received hydroxyurea immediately prior to enrollment in the study. Ten patients (29%) had diploid cytogenetics (3 with FLT3 mutations), 7 had chromosome 5 and/or 7 abnormalities; trisomy 8 was present in 2 patients and chromosome 11 abnormality in 1 patient. There was no patient with favorable cytogenetics.

Toxicities

The median number of cycles of treatment was 1 (range, 1–6). Eighteen (53%) patients received one cycle, 11 (32%) received 2 cycles and 5 (15%) patients received 3–6 cycles of therapy. In 15 out of the 29 (52%) patients who received ≤ 2 cycles, therapy was discontinued because of lack of response or disease progression. Other reasons included death of patients ($N = 8$), intercurrent infections ($N = 4$), patient's choice ($N = 2$) in face of relapsed/refractory disease. No Grade 4 non-hematological toxicity attributable to study drugs was encountered and no dose-limiting toxicity was seen. Grade 2/3 toxicities included vomiting (one patient), diarrhea (five patients), mucositis (two patients) and skin rash (one patient). Toxicities are summarized in Table III. Eight patients died while on study; 4 from sepsis, 2 from respiratory failure, 1 from intra-cranial hemorrhage and 1 from progressive disease. Sixteen patients required hospital admission for neutropenic fever during the course of the study.

Responses

Two patients (both 67 years of age) have achieved CR. Both patients were treated with high-dose 5-AC and high-dose cytarabine (Group 4). One patient with untreated AML (acute erythroleukemia) and a non-erythroid bone marrow blast percentage of 27%, associated with complex cytogenetics achieved CR after one cycle of treatment. Cytogenetic studies showed 1 out of 20 metaphases bearing pre-treatment abnormalities. After receiving three additional cycles of therapy, cytogenetics reverted to diploid before he proceeded with stem cell transplant in CR. The second patient with diploid cytogenetics and FLT3 mutation (both ITD and point mutation) was treated with three cycles of decitabine prior to study entry, last dose of decitabine being 4 weeks prior to study entry. He had no response to decitabine, had a starting marrow blast percentage was 67% and after three cycles of treatment on study drugs achieved hematologic improvement, which improved to a CR after five cycles. Currently, he has completed six cycles of therapy and after being in remission for 3 months relapsed with FLT3 mutation positive disease. In addition, two patients (one in group 3 and other in group 4) had reduction of blasts to below 10% without recovery of blood counts. Thus, in patients with relapsed/refractory disease, the response rate was 0%, while in minimally pre-treated patients, the response rate was 33%.

Discussion

In this clinical trial, we found that the simultaneous combination of 5-AC and cytarabine is safe and while good quality responses were observed in patients minimally pretreated with cytarabine, the response rate in relapsed/refractory AML was disappointing. Responses seen in minimally pre-treated patients could be attributable to the fact that these patients were not exposed to prior high-dose cytarabine. On the other hand, a critical factor for patients with relapsed/refractory disease was the limited number of cycles that were administered (median of 1). Disease progression and infectious complications related to their cytopenias precluded treatment beyond first cycle in majority of these patients. It has previously been shown that 5-AC requires multiple cycles for optimal activity [17], and the aggressiveness of AML in the refractory setting does not allow for optimal drug administration. In the future, the use of a hypomethylating agent to sensitize to cytotoxic therapy should consider the pace of the disease in the trial design. In a previous trial in refractory acute lymphocytic leukemia, the administration of a high dose of 5-AC was found to increase the levels of dCK. This was followed by high dose cytarabine, and CR was observed in 2/17 patients [29]. That trial suffered from the same problem of limited exposure to 5-AC, in a very aggressive disease.

Whether the synergy between 5-AC and cytarabine is schedule dependent is controversial. Although some pre-clinical studies support their concomitant administration [30], others have demonstrated antagonism with such a schedule [31]. Studies supporting sequential rather than concomitant administration of these agents suggest that pre-exposure of AML cells to 5-AC can restore dCK activity in AML cells and thus restore susceptibility to cytarabine. Concomitant administration of these agents may cause AML cells to enter into cell cycle arrest and reduce effectiveness of cytarabine as incorporation of ara-CTP to DNA will be impaired. One difficulty in interpreting the earlier *in vitro* studies is that most of them used a significantly higher concentration of 5-AC than is optimal for its hypomethylating activity. *In vitro* studies using decitabine showed that low doses of this hypomethylating agent are in fact synergistic with cytarabine when administered concurrently [24]. Nevertheless, it is possible that the limited clinical activity that we saw in our study among patients with relapsed/refractory AML may be because of antagonism of concomitant administration of both these agents. Ideally, the issue for resensitization to cytarabine by hypomethylation should be tested (i) in patients with relatively indolent relapses where multiple cycles can be administered, (ii) in a trial design that compares sequential and concurrent administration and (iii) in a trial that compares the combination to cytarabine alone to determine the synergistic/additive role of 5-AC.

This study demonstrates the feasibility of a new clinical trial design that seamlessly blends toxicity and efficacy studies across multiple doses [26]. The assumption that a higher dose is always better has been disproved in oncology [32], yet most phase II studies still test drugs at maximally tolerated dose. The trial design is potentially economical in that efficacy information gleaned in the phase I component is not wasted in the overall evaluation of the drug. In our study, the response rate was too low to take full advantage of this design. Nevertheless, most responses were seen in groups 3 and 4, which also accrued the highest number of patients, thus demonstrating the success of the adaptive randomization. This trial design is worth considering in clinical trials where a limited number of doses or dose combinations will be explored.

In conclusion, the combination of 5-AC with cytarabine is safe, active in patients with AML and minimal prior therapy but has limited clinical efficacy in patients with relapsed, refractory AML particularly in a population where multiple administrations of therapy is not possible. Additional trials with patients with less proliferative and less pre-treated disease may better define the efficacy of this combination.

Acknowledgments

This study was supported by a National Institutes of Health grant CA100632 and by a grant from Celgene Corporation. JPI is an American Cancer Society Clinical Research Professor supported by a generous gift from the F. M. Kirby Foundation.

References

1. Teodoridis JM, Strathdee G, Brown R. Epigenetic silencing mediated by CpG island methylation: potential as a therapeutic target and as a biomarker. *Drug Resist Update* 2004;7:267–278.
2. Fojo T, Bates S. Strategies for reversing drug resistance. *Oncogene* 2003;22:7512–7523. [PubMed: 14576855]
3. Kroeger H, Jelinek J, Estecio MR, et al. Aberrant CpG island methylation in acute myeloid leukemia is accentuated at relapse. *Blood* 2008;112:1366–1373. [PubMed: 18523155]
4. Agrawal S, Unterberg M, Koschmieder S, et al. DNA methylation of tumor suppressor genes in clinical remission predicts the relapse risk in acute myeloid leukemia. *Cancer Res* 2007;67:1370–1377. [PubMed: 17283175]
5. Issa JP. DNA methylation as a therapeutic target in cancer. *Clin Cancer Res* 2007;13:1634–1637. [PubMed: 17363514]
6. Lee T, Karon M, Momparler RL. Kinetic studies on phosphorylation of 5-azacytidine with the purified uridine-cytidine kinase from calf thymus. *Cancer Res* 1974;34:2482–2488. [PubMed: 4137739]
7. Grant S, Cadman E. Altered 5-azacytidine metabolism following 3-deazauridine treatment of L5178Y and human myeloblasts. *Cancer Res* 1980;40:4000–4006. [PubMed: 6162541]
8. Plagemann PG, Behrens M, Abraham D. Metabolism and cytotoxicity of 5-azacytidine in cultured Novikoff rat hepatoma and P388 mouse leukemia cells and their enhancement by preincubation with pyrazofurin. *Cancer Res* 1978;38:2458–2466. [PubMed: 78761]
9. Cihak A, Vesely J, Skoda J. Azapyrimidine nucleosides: metabolism and inhibitory mechanisms. *Adv Enzyme Regul* 1985;24:335–354. [PubMed: 2424284]
10. Cihak A, Vesely J, Sorm F. Incorporation of 5-azacytidine into liver ribonucleic acids of leukemic mice sensitive and resistant to 5-azacytidine. *Biochim Biophys Acta* 1965;108:516–518. [PubMed: 5867538]
11. Weiss JW, Pitot HC. Effects of 5-azacytidine on nucleolar RNA and the preribosomal particles in Novikoff hepatoma cells. *Biochemistry* 1975;14:316–326. [PubMed: 47243]
12. Cihak A. Biological effects of 5-azacytidine in eukaryotes. *Oncology* 1974;30:405–422. [PubMed: 4142650]
13. Mohandas T, Sparkes RS, Shapiro LJ. Reactivation of an inactive human X chromosome: evidence for X inactivation by DNA methylation. *Science* 1981;211:393–396. [PubMed: 6164095]
14. Jones PA, Taylor SM. Cellular differentiation, cytidine analogs and DNA methylation. *Cell* 1980;20:85–93. [PubMed: 6156004]
15. Creusot F, Acs G, Christman JK. Inhibition of DNA methyltransferase and induction of friend erythroleukemia cell differentiation by 5-azacytidine and 5-aza-2'-deoxycytidine. *J Biol Chem* 1982;257:2041–2048. [PubMed: 6173384]
16. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol* 2006;24:3895–3903. [PubMed: 16921040]
17. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *J Clin Oncol* 2002;20:2429–2440. [PubMed: 12011120]
18. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009;10:223–232. [PubMed: 19230772]
19. Schroder JK, Kirch C, Seeber S, Schutte J. Structural and functional analysis of the cytidine deaminase gene in patients with acute myeloid leukaemia. *Br J Haematol* 1998;103:1096–1103. [PubMed: 9886326]

20. Steuart CD, Burke PJ. Cytidine deaminase and the development of resistance to arabinosyl cytosine. *Nat New Biol* 1971;233:109–110. [PubMed: 5285962]
21. Gati WP, Paterson AR, Larratt LM, Turner AR, Belch AR. Sensitivity of acute leukemia cells to cytarabine is a correlate of cellular es nucleoside transporter site content measured by flow cytometry with SAENTA-fluorescein. *Blood* 1997;90:346–353. [PubMed: 9207471]
22. Colly LP, Peters WG, Richel D, Arentsen-Honders MW, Starrenburg CW, Willemze R. Deoxycytidine kinase and deoxycytidine deaminase values correspond closely to clinical response to cytosine arabinoside remission induction therapy in patients with acute myelogenous leukemia. *Semin Oncol* 1987;14(2 Suppl 1):257–261. [PubMed: 3035720]
23. Bhalla K, Nayak R, Grant S. Isolation and characterization of a deoxycytidine kinase-deficient human promyelocytic leukemic cell line highly resistant to 1- β -D-arabinofuranosylcytosine. *Cancer Res* 1984;44:5029–5037. [PubMed: 6091869]
24. Qin T, Youssef EM, Jelinek J, et al. Effect of cytarabine and decitabine in combination in human leukemic cell lines. *Clin Cancer Res* 2007;13:4225–4232. [PubMed: 17634552]
25. Qin T, Jelinek J, Si J, Shu J, Issa JP. Mechanisms of resistance to 5-aza-2'-deoxycytidine in human cancer cell lines. *Blood* 2009;113:659–667. [PubMed: 18931345]
26. Huang X, Biswas S, Oki Y, Issa JP, Berry DA. A parallel phase I/II clinical trial design for combination therapies. *Biometrics* 2007;63:429–436. [PubMed: 17688495]
27. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* 2003;21:4642–4649. [PubMed: 14673054]
28. Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood* 2000;96:3671–3674. [PubMed: 11090046]
29. Avramis VI, Mecum RA, Nyce J, Steele DA, Holcenberg JS. Pharmacodynamic and DNA methylation studies of high-dose 1- β -D-arabinofuranosyl cytosine before and after *in vivo* 5-azacytidine treatment in pediatric patients with refractory acute lymphocytic leukemia. *Cancer Chemother Pharmacol* 1989;24:203–210. [PubMed: 2473850]
30. Neil GL, Berger AE, Bhuyan BK, DeSante DC. Combination chemotherapy of L1210 leukemia with 1- β -D-arabinofuranosylcytosine and 5-azacytidine. *Cancer Res* 1976;36:1114–1120. [PubMed: 56229]
31. Momparler RL, Goodman J, Karon M. *In vitro* biochemical and cytotoxicity studies with 1- β -D-arabinofuranosylcytosine and 5-azacytidine in combination. *Cancer Res* 1975;35:2853–2857. [PubMed: 50882]
32. Issa JP, Garcia-Manero G, Giles FJ, et al. Phase 1 study of low-dose prolonged exposure schedules of the hypomethylating agent 5-aza-2'-deoxycytidine (decitabine) in hematopoietic malignancies. *Blood* 2004;103:1635–1640. [PubMed: 14604977]

Table I

Treatment groups.

	5-AC	Cytarabine
Group 1	37.5 mg/m ² /day IV over 20–30 min daily ×7	100 mg/m ² /day continuous intravenous infusion (CIV) ×7 days
Group 2	75 mg/m ² /day IV over 20–30 min daily ×7	100 mg/m ² /day continuous intravenous infusion (CIV) ×7 days
Group 3	37.5 mg/m ² /day IV over 20–30 min daily ×7	1g/m ² /day CIV days 1–4 (age <65 years) or days 1–3 (age ≥65 years)
Group 4	75 mg/m ² /day IV over 20–30 min daily ×7	1g/m ² /day CIV days 1–4 (age <65 years) or days 1–3 (age ≥65 years)

Table II

Patient characteristics.

	<i>N</i> = 34	
Parameters	<i>N</i> (%)	
Diagnosis		
Relapsed or refractory AML	32	(94)
Untreated AML	2	(6)
Cytogenetics		
Diploid	10	(29)
Poor-risk	24	(71)
Ft3 Mutation	3	
Prior AHD	7	(21)
	Median or <i>N</i>	Range
Age, years	62	31–79
WBC	4.1	0.5–148.4
Hemoglobin	9.5	7.1–13.2
Platelets	38.5	10–196
No. of prior therapies	2	0–6
Hypomethylating agent	9	
High-dose cytarabine	21	

AML, acute myelogenous leukemia; AHD, antecedent hematological disorder.

Table III

Toxicities.

<hr/>		
	<i>N</i> = 34	
<hr/>		
	<i>N</i> (%)	
<hr/>		
Deaths while on study	8 (24)	
Neutropenic fever	16 (47)	
<hr/>		
Drug related toxicities	Grade 2	Grade 3/4
<hr/>		
Diarrhea	5 (15)	
Mucositis		2 (6)
Vomiting	1 (3)	
Rash	1 (3)	
<hr/>		