Original Article

Phase 2 Randomized Study of p53 Antisense Oligonucleotide (Cenersen) Plus Idarubicin With or Without Cytarabine in Refractory and Relapsed Acute Myeloid Leukemia

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BACKGROUND: The p53 antisense oligonucleotide cenersen has been shown to sensitize acute myeloid leukemia (AML) stem cells to DNA damaging agents. **METHODS:** To determine whether cenersen merits testing in larger efficacy studies, an exploratory study of cenersen in combination with idarubicin either alone or with 1 of 2 doses of cytarabine was performed in first-salvage AML patients. Patients who either had failed to respond to a single induction course or had responded to induction but relapsed within 12 months were enrolled. Stopping rules based on an expected 14% complete response (CR) rate were applied to each treatment arm. **RESULTS:** Fifty-three patients were treated, and none of the arms was terminated for lack of activity. Nearly all patients received a single course unless they responded. Ten of the 53 (19%) patients responded (8 CR and 2 CR with incomplete platelet recovery). There was a positive trend for a better response rate with increasing intensity of chemotherapy in the patients refractory to front-line treatment compared with those who had relapsed previously. One-third (17/53) of the patients received cenersen inhibitors (acetaminophen and/or high dose antioxidants) during treatment, and none of these responded to treatment. No unique toxicity was attributed to cenersen. **CONCLUSION:** The results of this study suggested that the combination of cenersen with chemotherapy may have clinical efficacy, and additional studies are warranted to explore its full potential. ***Cancer* 2012;118:418–27.** *© 2011 American Cancer Society.*

KEYWORDS: acute myeloid leukemia, refractory, relapsed, p53, antisense, cenersen.

INTRODUCTION

The normal function of p53 includes protection from the effects of DNA damage and/or proto-oncogene activation by directing defective cells to undergo either p53-dependent programmed cell death (both stimuli) or p53-dependent cell cycle arrest and repair (DNA damage only).[1] Consequently, if a premalignant cell is to progress to a full malignant phenotype, it must inhibit p53-dependent programmed cell death.[2-5] In contrast, p53-dependent cell cycle arrest and repair function appear to be frequently retained in cancer cells with wild-type p53.[1,6,7] When p53 mutates, this protective function is lost but can be compensated for via gain-of-function mutant p53.[8-11]

Cenersen is an antisense oligonucleotide that blocks the production of both wild-type and mutant p53 to produce anticancer effects.[12-14] It has a ribonuclease H (RNase H)–dependent mechanism of action that causes the p53 messenger RNA to be cleaved at the site to which cenersen binds.[14] In acute myeloid leukemia (AML), cenersen has preferential activity against the malignant stem cells and some of the more mature progenitor cells, probably because they express high levels of RNase H.[15-17] Cenersen sensitizes these AML cells, at least when they are in cycle, to atmospheric oxygen and to low

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Table 1. Summary of Treatment Groups

Group	Cenersen	Idarubicin	Ara-C
1	2.4 mg/kg days 1-4	12 mg/m^2 days 2-4	None
2	2.4 mg/kg days 1-4	12 mg/m^2 days 2-4	100 mg/m^2 days 2-8
3	2.4 mg/kg days 1-4	12 mg/m^2 days 2-4	1 g/m^2 days 2-5 (or 1 g/m^2 days 2-4 if age $\geq$60 y)

levels of many different DNA-damaging agents, including chemotherapeutic agents used at doses that have minimal or no effect on leukemic cells in the absence of cenersen.[15]

In this study, we focused on patients who were either refractory to a single intensive front-line course of induction chemotherapy or who had relapsed <12 months after frontline treatment. Historical data show that the expected complete response (CR) rate for each of these groups is 14% when treated with high-dose (1 g/m^2) cytarabine-containing regimens.[18] The primary objective was to determine the efficacy of cenersen in combination with idarubicin and either no cyctarabine or 1 of 2 different doses (100 mg/m^2 or 1 g/m^2) of cytarabine.

MATERIALS AND METHODS

Cenersen

Cenersen is the United States Adopted Name and International Nonproprietary Name of a 20-mer phosphorothioate oligonucleotide that is complementary to a portion of the coding sequence in p53 messenger RNA. The specific nucleotide sequence is 5′-d[P-Thio](CCCTG CTCCC CCCTG GCTCC)- 3′.

Study Design

This was an open-label, phase 2a, randomized 3-arm study involving treatments of increasing chemotherapy intensity in combination with cenersen in first-salvage AML patients $\geq$18 years old. The trial was conducted using a selection design that uses Bayesian principles to provide good frequentist properties to establish a probability of selecting the truly active therapy regimens among those tested by rejecting any truly ineffective regimen. To be eligible, patients were required to be refractory to 1 induction chemotherapy course or to have obtained a CR lasting <12 months and to have received no other salvage therapy. Other eligibility criteria included performance status of 0-2 and adequate organ function. The study was approved by the institutional review boards of the participating institutions, and all patients signed informed consent.

The primary end point was CR rate. Historical data (MD Anderson Cancer Center, 1991- 2001) indicate that the probability of CR for the subset of first-salvage patients meeting the entry criteria for this study is 14%. The most intensive (group 3) chemotherapy given in the current study is equivalent to the cytarabine regimens given to nearly 70% of the patients used to generate the historical control.

Treatment Plan

The treatment plan is summarized in Table 1. Patients received therapy with cenersen via continuous intravenous infusion (CIV) daily for 4 consecutive days. On the second day of cenersen administration, patients started a 3-day course of idarubicin 12 mg/m^2/day while continuing therapy with cenersen. In addition, patients were randomized to receive no cytarabine, a daily dose of 100 mg/m^2 cytarabine CIV for 7 consecutive days, or 1 g/m^2 daily CIV for 4 consecutive days (3 days for patients $\geq$60 years of age). These schedules were selected to investigate the optimal schedule of cytarabine to be used in combination with cenersen and idarubicin in subsequent studies.

Patients not achieving remission after 1 course were scheduled to receive a second course of induction chemotherapy with the same schedule as the first course. Patients who achieved a response after 1 or 2 courses were eligible to receive additional courses of the same regimen up to a total of 6 at a frequency determined by the treating physician. Patients received supportive care, antimicrobials, and other medications as required. Concomitant administration of acetaminophen and high-dose antioxidants was prohibited by the protocol from 1 day before the start of cenersen infusion through the end of day 6 of treatment for a total of 7 days.

Patients underwent physical examination, complete blood count, blood chemistry evaluation, bone marrow aspiration, and cytogenetic analysis before the start of therapy. During and after chemotherapy, patients were followed with complete blood count and blood chemistry at least once weekly, and a bone marrow aspiration was scheduled on day 28 and then as clinically indicated to assess response. Cytogenetic abnormalities were classified according to the Medical Research Council criteria[19] as those conferring favorable prognosis, [t(8:21)(q22;q22)

and inv(16)], intermediate risk (diploid, +21, +22, +4, and +8), and adverse risk (all others), and complex karyotype was defined as ≥3 abnormalities. Response to therapy was assessed using the definitions proposed by the International Working Group.[20]

Statistical Analysis

After the initial sequential entry of 3 patients per dose group (Table 1), the remaining patients were randomly assigned to each of the 3 treatment groups. The outcome of interest was CR. Historical data from the MD Anderson Cancer Center indicated that the probability of CR among patients who failed a single induction course or whose first CR lasted <12 months is 14% (52/372). Denoting the probability of CR by $\theta_{CR/H}$, we assumed that $\theta_{CR/H}$ follows a (0.3, 1.7) beta distribution; this distribution has a mean of 0.15. We assumed that each of the experimental treatment probabilities $\theta_{CR/E1}$, $\theta_{CR/E2}$, and $\theta_{CR/E3}$ follow the same distribution [ie, beta (0.3, 1.7)]. The early stopping rules were to terminate treatment within each experimental arm if, compared with the historical experience, that arm's CR rate is unlikely to increase by a mean of 0.15. This rule was applied in each experimental arm after each cohort of 5 patients, up to a maximum of 15 per arm, was evaluated. The stopping bounds generated by these rules were designed to terminate accrual to an arm if the CR rate was ≤0/5, 1/10, 2/15, 3/20, 3/25, 4/30, 5/35, or 5/40. The sample sizes above 15 (3/20 etc.) refer to the possibility that at least 1 arm would be terminated early, with accrual continuing beyond 15 on the remaining arms.

All patients receiving at least 1 dose of cenersen constituted the intent-to-treat (ITT) population.

Ad Hoc Analyses and Definition of Per-Protocol Subpopulation

Preclinical data suggested that use of acetaminophen or antioxidants could adversely affect the potential benefit of cenersen therapy. Although use of these agents was not allowed by the protocol during treatment, 32% (17/53) of the patients in the present study received acetaminophen (n = 11), high-dose antioxidants (n = 3), or both (n = 3) during times specified by the protocol. In addition to the 17 patients who received prohibited substances, 4 patients failed to meet the protocol entry criteria (2 patients had multiple previous treatment failures; 1 patient had myelofibrosis at study entry, screening bone marrow <5% blasts, and disease that could not be monitored by bone marrow analysis; and 1 patient received chemotherapy (hydroxyurea) within 2 days from the start of study drug. Hydroxyurea can cause p53 to undergo posttranslational modifications that dramatically increase its half-life. Accordingly, a per-protocol population was defined for subset analysis that excluded the patients just described.

An ad hoc analysis was undertaken to determine the effect, if any, of the use of acetaminophen and/or high-dose antioxidants on the ability of a cenersen containing regimen (cenersen regimen) to induce a response (CR or complete response with incomplete platelet recovery [CRp]). To achieve this, 11 of the 53 treated patients who were inappropriate for this particular analysis were censored (4 did not meet entry criteria and 7 could not be analyzed for response [5 due to early death and 2 due to uninterpretable bone marrow results]). Of the remaining 42 patients, 14 received substances prohibited by the protocol (8 acetaminophen, 3 high-dose antioxidants, and 3 both) during specified times and 28 did not. Thus, 3 of the 17 patients who received prohibited substances could not be evaluated for response and were, therefore, not used in this analysis.

RESULTS

Patient Characteristics

The patient characteristics for the overall ITT population for each of the treatment groups are shown in Table 2. The ITT and per protocol populations had an identical median age of 58 years (range, 19-88 years). There were no significant differences among the treatment groups 1, 2, or 3 with respect to sex, age, race, or cytogenetics. Nineteen of the ITT patients (36%) were previously unresponsive to a single front-line induction course, and 34 (64%) had relapsed from front-line therapy in <12 months. Cytogenetic analysis was available for 49 patients, and of these 57% had intermediate, 35% had adverse, and 8% had favorable risk cytogenetic abnormalities.

Response to Treatment

Considering the ITT population, there were 13 patients in arm 1, 21 in arm 2, and 19 in arm 3. None of the 3 treatment groups triggered the prospectively defined stopping rules that were established to eliminate treatments that did not at least match the historical control of a 14% CR rate. The ITT response rates by treatment group are shown in Table 3. There appeared to be a trend toward better results with increasing intensity of chemotherapy culminating in a 21% (4/19) CR rate in group 3. Among all 3 treatment groups, 10 patients responded to therapy

Table 2. Patient Characteristics at Study Entry: Intent-to-Treat Population

Patient Cohort	Age, y	Response to Front-Line Drug, No.	Cytogenetics, No.[a]	Performance Status	WBCs, $\times 10^9$/L	Platelets, $\times 10^9$/L	Peripheral Blood Blasts, %	BM Blasts, %
Overall	58 (19-88)	Refractory: 19 Relapsed: 34	Favorable: 4 Intermediate: 28 Adverse: 17	1 (0-3)	3.3 (0.3-279.6)	43 (5-659)	14.5 (0-97)	38 (4-100)
Group 1	63 (19-88)	Refractory: 5 Relapsed: 8	Favorable: 1 Intermediate: 8 Adverse: 3	1 (0-2)	3.0 (1-279.6)	45 (11-659)	14 (0-87)	26 (12-92)
Group 2	58 (25-81)	Refractory: 6 Relapsed: 15	Favorable: 1 Intermediate: 10 Adverse: 8	1 (0-2)	3.6 (0.3-84.7)	27 (5-642)	13 (0-92)	45 (4-100)
Group 3	52 (25-76)	Refractory: 8 Relapsed: 11	Favorable: 2 Intermediate: 10 Adverse: 6	0 (0-3)	2.9 (1.1-66.6)	43 (8-361)	23 (0-97)	36 (8-89)

Abbreviations: BM, bone marrow; WBCs, white blood cells.
Data are presented as median (range) unless specified otherwise.
[a] Four patients have no available data: group 1 (n = 1), group 2 (n = 2), group 3 (n = 1).

Table 3. Remission Rates by Treatment Group (Intent-to-Treat)

Overall (N = 53)		Group 1 (n = 13)		Group 2 (n = 21)		Group 3 (n = 19)	
CR	CR+CRp	CR	CR+CRp	CR	CR+CRp	CR	CR+CRp
8 (15)	10 (19)	1 (8)	2 (15)	3 (14)	4 (19)	4 (21)	4 (21)

Abbreviations: CR, complete response; CRp, complete response with incomplete platelet recovery.
Data are presented as no. (%).

(CR rate, 15% [8/53]; CR + CRp rate, 19% [10/53]). The previous therapy received by patients with response to cenersen-based therapy is presented in Table 4.

Table 5 shows the response rates by treatment group for the per-protocol population. The response rates of each corresponding group appear to be better than those seen in the ITT analysis (Table 3). The number of responders either within or between groups, however, is too small to meaningfully test differences by cytarabine intensity. The best outcome was seen in group 3, in which the per-protocol CR rate was 36%, whereas there was 1 CR (13%) and 1 CRp in the 8 evaluable patients in group 1 (25%) and 3 CR (23%) and 1 CRp in the 13 evaluable patients in group 2 (31%).

The results of the ad hoc analysis to determine what effect the use of acetaminophen and/or high-dose antioxidants had, if any, on response to a cenersen regimen is shown in Table 6. All 10 responders in this study were found to be in the group of 28 evaluable patients who did not receive these substances during treatment, whereas none of the 14 patients who received these substances during treatment responded ($P = 0.0174$; 95% confidence interval, 7.5%-62.6%).

The ratio of patients in this study who were nonresponsive to a single induction course versus those relapsing <12 months after induction treatment was in the expected range. A disproportionate number of the group refractory to front-line treatment (60%) responded to therapy with cenersen (Table 7). This trend is seen in both the ITT (CR, 26% vs 9%; CR + CRp, 32% vs 12%) and the per-protocol populations (CR, 38% vs. 16%; CR + CRp, 46% vs 21%). Two of the responses to cenersen-based therapy among the patients unresponsive to front-line induction therapy occurred in group 1, 1 occurred in group 2, and 3 occurred in group 3 (Table 4).

Duration of Remissions and Survival

After a median follow-up of 18.5 months from start of therapy, 2 patients remain alive and in CR. The median duration of response for all 10 responding patients was 7.9 months (range, 2-24). Patients received a median of 1 course of therapy, with 12 patients receiving 2 or more courses of therapy (7 of these were responders). After achieving remission, 7 patients underwent stem cell transplantation. The median duration of the response to a cenersen regimen for nontransplant patients (n = 3) was 11.2

Table 4. Previous Treatments Given to Responders

Front-Line Treatment	Response to Front-Line Treatment	Cenersen Treatment Group	Response to Cenersen Regimen
Daunorubicin, 60 mg/m^2/d, days 1-3 Cytarabine, 200 mg/m^2/d, days 1-7	Refractory	1	CRp
PKC 412, 200 mg/d, days 8-31 Daunorubicin, 60 mg/m^2/d, days 1-3 Cytarabine, 200 mg/m^2/d, days 1-7 PKC 412, 200 mg/d, days 1-31	Refractory	1	CR
Idarubicin, 12 mg/m^2/d, days 1-3	Relapse	2	CR
Cytarabine, 1.5 g/m^2/d, days 1-4 **Then as consolidation:** **Cytarabine, 100 mg/m^2/d ×5 days** **Idarubicin, 8 mg/m^2/d +** **Cytarabine, 1.5 g/m^2/d ×2 days** **Cytarabine, 100 mg/m^2/d ×5 days**			
Daunorubicin (20 mg/m^2/d ×4 d) ×2 Cytarabine (200 mg/m^2/d ×4 d) ×2 Etoposide (100 mg/m^2/d ×4 d) ×2 Thioguanine (100 mg/m^2/d ×4d) ×2 Dexamethasone (6 mg/m^2/d ×4 d) ×2 Cytarabine intrathecal (70 mg) ×2	Relapse	2	CRp
Idarubicin, 12 mg/m^2/d, days 4-6 Cytarabine, 1.5 g/m^2/d, days 4-7	Refractory	3	CR
Daunorubicin, 45 mg/m^2/d, days 1-3 Cytarabine, 100 mg/m^2/d, days 1-8 Zosuquidar, 700 mg/d, days 1-3	Refractory	3	CR
Daunorubicin[a] ×3 days Cytarabine[a] ×7 days	Refractory	3	CR
Idarubicin, 12 mg/m^2/d ×3 days Cytarabine, 100 mg/m^2/d, ×7 days	Refractory	2	CR
Daunorubicin, 90 mg/m^2/d, days 1-3 Cytarabine, 100 mg/m^2/d, days 1-7	Relapsed	2	CR
Etoposide, 100 mg/m^2/d, days 1-3 **Then as consolidation: HIDAC ×3 courses**			
Idarubicin[a] Cytarabine[a]	Relapsed	3	CR
Etoposide[a] **Then as consolidation: HIDAC[a]**			

Abbreviations: CR, complete response; CRp, complete response with incomplete platelet recovery; HIDAC, high-dose Ara-C.
[a] Dose unknown.

Table 5. Remission Rates by Treatment Group (Per-Protocol)

Overall (N = 32)		Group 1 (n = 8)		Group 2 (n = 13)		Group 3 (n = 11)	
CR	CR+CRp	CR	CR+CRp	CR	CR+CRp	CR	CR+CRp
8 (25)	10 (31)	1 (13)	2 (25)	3 (23)	4 (31)	4 (36)	4 (36)

Abbreviations: CR, complete response; CRp, complete response with incomplete platelet recovery.
Data are presented as no. (%).

versus 6.6 months for those who received a transplant (n = 7).

The median survival for the total patient population was 5.3 months (range, 0.3-26.8) and 6.3 months (range, 0.3-26.8) for the per-protocol population (Figure 1). Survival estimates for the 3 treatment groups are shown in Figure 2. Seven patients (13%) died during induction (ie, during the 30 days immediately after the start of chemotherapy), with the cause of death reported as respiratory failure (n = 3), cardiopulmonary arrest (n = 2), sepsis (n = 1), and intracranial hemorrhage (n = 1).

Table 6. Lack of Use of Cenersen Inhibitors Is Associated With Obtaining a Response in Patients With an Evaluable BM and Meeting Entry Criteria

Administration of Prohibited Substances (No. of Patients)	Responses		*P*
	CR+CRp	No Response	
Yes (14)	0	14	0.0174
No (28)	10	18	

Abbreviations: CR, complete response; CRp, complete response with incomplete platelet recovery.

Six of the 10 responding patients had been refractory to their front-line treatment. Of these, the average duration of response after a cenersen regimen was 7.6 months (range, 2.3-24.5 months). The average response duration for the patients responding to their original front-line treatment was 9.7 months (range, 5.9-12.2 months) compared with 8.4 months (range, 5.4-11.6 months) after salvage treatment with cenersen. The 2 relapsed patients who had a shorter response duration after a cenersen regimen (220 and 163 days) compared with that following front-line treatment (366 and 343 days) died shortly following transplantation.

Safety Results

The frequency of adverse events in this trial appears to be similar across the treatment groups, with the exception of diarrhea, constipation, abdominal pain, febrile neutropenia, rash, headache, dizziness, and vomiting, which showed a dose–response relationship with increasing cytarabine doses.

The most common treatment-emergent adverse events, regardless of causality, are presented in Table 8. A total of 13 (35%) patients died during the study (ie,

Table 7. Cenersen Regimen Remission Rates by Response to Front-Line Treatment

Response to Front-Line Treatment	Intent-to-Treat		Per-Protocol	
	CR	CR+CRp	CR	CR+CRp
Refractory	5/19 (26)	6/19 (32)	5/13 (38)	6/13 (46)
Relapsed	3/34 (9)	4/34 (12)	3/19 (16)	4/19 (21)

Abbreviations: CR, complete response; CRp, complete response with incomplete platelet recovery.
Data are presented as no. with response/no. evaluable (%).

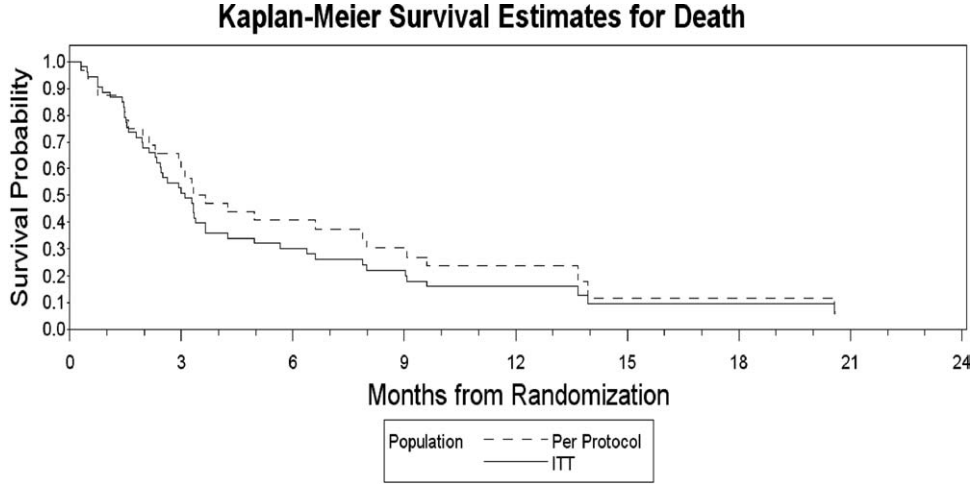

Figure 1. Comparison of the Kaplan-Meier survival estimates for the ITT and per-protocol populations is shown.

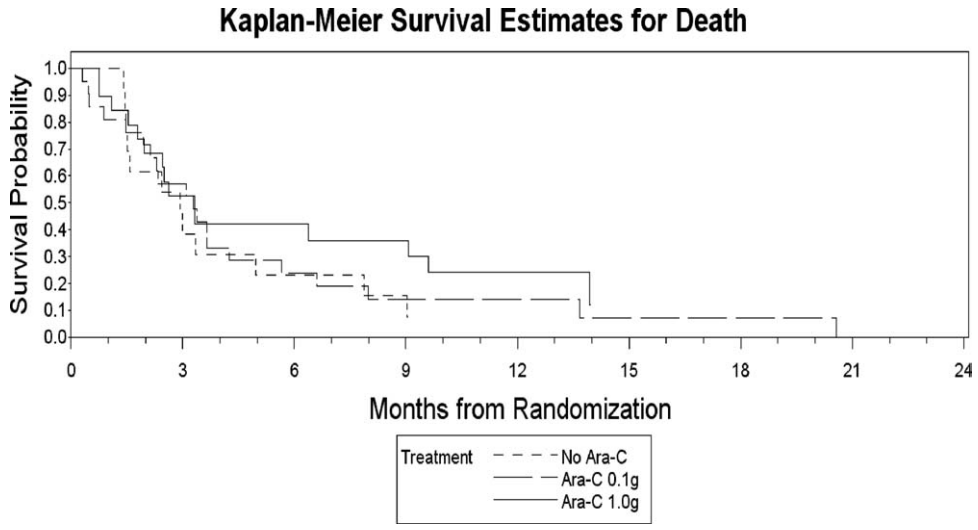

Figure 2. Comparison of the Kaplan-Meier survival estimates for all 3 treatment arms is shown.

Table 8. Most Common Treatment-Emergent Adverse Events

Adverse Event	% of Patients
Nausea	68
Diarrhea	66
Hypokalemia	66
Febrile neutropenia	60
Fatigue	53
Hypomagnesaemia	49
Constipation	42
Cough	42
Rash	40
Pyrexia	38
Dyspnoea	36
Chills	34
Headache	34
Abdominal pain	32
Vomiting	32
Edema peripheral	28
Hypocalcaemia	25
Insomnia	25
Anxiety	23
Epistaxis	23
Petechiae	23
Anorexia	21
Hyperbilirubinemia	21
Hypotension	21

Cenersen ELP1001 data (n =53) are presented and include adverse events ocurring in ≥20% of patients.

within 30 days of the last dose of cenersen). The causes of death included respiratory failure/arrest (n = 3); cardiopulmonary arrest (n = 3); progressive disease (n = 2); and septic shock, multiorgan failure, sepsis, intracranial hemorrhage, and unknown cause (n = 1 each).

Because idarubicin was included in all arms of therapy in this study, the frequency of adverse events seen in this study was compared with the frequency of adverse events described in the Idamycin package insert. Several differences were observed in the most common toxicities between those observed in this study and those reported in the package insert for idarubicin used in combination with the cytarabine regimen used for group 2: mucositis (34% vs 50%), hemorrhage (30% vs 63%), hair loss (13% vs 77%), and nausea and vomiting (68% vs 82%).

DISCUSSION

In phase 1 testing, cenersen was used as a single agent over 5 dose levels to treat 16 patients with AML or advanced myelodysplasia.[21] Cenersen demonstrated similar pharmacokinetics to other phosphorothioates, and no specific toxicities were attributed to its administration. There were no clinical responses. It was expected at the time that cenersen would have activity as a single agent based on in vitro studies. It was subsequently found, however, that atmospheric oxygen was supplying sufficient genomic damage to allow for the antileukemic effect of cenersen in vitro. Furthermore, it was shown that low-dose anthracyclines could replace the elevated oxygen level as a source of genomic damage.[15]

The current phase 2a study was undertaken to clinically test the demonstrated need to combine a p53 inhibitor with a genome damaging agent to enhance the killing of cancer cells with wild-type p53.[13,14,22-25] The statistical design of the study provided for the elimination of any of the 3 treatment arms that did not meet a predetermined response rate. A total of 53 patients were treated in this

study, and none of the treatment arms was terminated. In 2 of the treatment arms, the intensity of the chemotherapy was less than that used to generate the historical control data. The CR rate in the ITT population was 15%, with a trend toward an improving CR rate with increasing dose of cytarabine (8%, 14%, and 21%). Thus, the primary end point for the ITT population was not different than the 14% historical control. However, we have insufficient information to determine whether there is a true difference in response by cytarabine dose, particularly when considering only patients treated per protocol.

Given the frequent use of prohibited substances in this study, an ad hoc per-protocol population was defined for the purpose of a subset analysis. This per-protocol population primarily excluded patients who received the substances prohibited by the protocol for use during treatment but also excluded patients who could not be evaluated for response or who did not meet the entry criteria.

The protocol precluded the use of acetaminophen and high-dose antioxidants during treatment, because these agents had been shown in vitro to block the antileukemia effect of cenersen. Human AML cell lines and peripheral blood mononuclear cells express cytochrome P450 that converts acetaminophen to the highly reactive metabolite *n*-acetyl-*p*-benzoquinoneimine (NAPQI).[27,28] NAPQI also has been shown to covalently bind to endogenous DNA in vivo but at low frequency.[29] NAPQI alkylates cenersen and other phosphorothioates at multiple sites but not oligonucleotides with a phosphodiester linkage.[30] Thus, this alkylation mostly likely occurs on the nonbridging sulfur in the phosphorothioate linkage.

Antioxidants scavenge free radicals that exhibit antileukemia effects on freshly obtained AML blasts when combined with cenersen. In addition, a wide variety of antioxidants can induce p21 independently of p53 and thereby cause cell cycle arrest.[31-35] A key component of cenersen's potential to sensitize cancers with wild-type p53 to conventional cancer therapeutics is its ability to prevent p53-dependent cell cycle arrest and repair activated by DNA-damaging agents.[32-35] Failure to arrest proliferation allows the cancer cells to replicate their damaged DNA and, in turn, activate p53-independent programmed cell death. High-dose antioxidants could stop this process by causing cell cycle arrest and inhibiting the therapeutic effect of cenersen.

Three lines of evidence based on comparisons between subgroups of the treated patients suggest possible positive trends, supportive of the notion that cenersen might be active in AML. First, the analysis showed that the use of prohibited cenersen inhibitors during treatment was associated with no responses in the 14 patients who received 1 or both of these substances and who could be evaluated for response. In contrast, all 10 of the responders were in the group of 28 per-protocol patients who could be evaluated for response and who did not receive these prohibited substances. Thus, there was a positive trend for a correlation between treatment failure and the administration of cenersen inhibitors ($P = .0174$).

Second, the response rate in the ITT group was highest among patients refractory to a single course of induction chemotherapy (CR, 26%; CR + CRp, 32%) compared with the response rate (CR, 9%; CR + CRp, 12%) for relapsed patients. In the per-protocol group, the respective CR rates for these 2 groups were refractory CR 38% (46% CR + CRp) versus relapsed CR 16% (21% CR + CRp). Based on historical controls, these 2 groups were expected to have the same CR rate for a subsequent course of treatment.[18,36] It is possible, however, that the remissions achieved could have been achieved with the same chemotherapy without cenersen. Randomized studies would be required to further evaluate the possible contribution of cenersen to the responses observed in this patient population.

Third, 8 of the 10 patients achieving a CR or CRp in this study either had been unresponsive to front-line treatment or had responses that lasted longer than the responses they had to previous front-line treatment, suggesting that the addition of cenersen to chemotherapy may contribute to achieving or obtaining an increased duration of response. There were responders in all 3 treatment groups. The 7 responders who underwent transplantation had a shorter median duration of response than the 3 responders who did not. This suggests the improvement in response duration following administration of a cenersen regimen was not due to transplantation. The 2 patients who had a shorter response duration compared with that following front-line treatment died after transplantation. Thus, the brevity of their response duration may not be attributable to the cenersen regimen.

Numerous studies have established that blocking p53 function by various means protects a wide variety of normal cells from the toxic effects of chemotherapy or radiation.[37-40] In this study, there was no evidence that the addition of cenersen increased the toxicity expected from chemotherapy alone, and no unique toxicity could be attributed to cenersen. Subsequent controlled trials involving cenersen should seek to more precisely define

any role cenersen may have in protecting patients from adverse events resulting from cytotoxic therapies.

The adverse event profiles in this study were both qualitatively and quantitatively within the expected ranges for these chemotherapeutic regimens in first-salvage patients.[26] This small study failed to signal attribution of specific or unique toxicities to cenersen.

In conclusion, the combination of cenersen with idarubicin, with or without cytarabine, is well tolerated. The preclinical data and the results presented here suggest that this combination could potentially have a role in the management of AML. To achieve the optimal potential benefit of cenersen in this context, avoidance of antioxidants and acetaminophen are required. A placebo-controlled randomized trial is required to determine the clinical contribution of cenersen in this setting.

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CONFLICT OF INTEREST DISCLOSURES

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