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ORIGINAL REPORT

Multicenter, Phase II Study of Decitabine for the First-Line Treatment of Older Patients With Acute Myeloid Leukemia

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A B S T R A C T

Purpose
Older patients with acute myeloid leukemia (AML) have limited treatment options because of the lack of effectiveness and the toxicity of available therapies. We investigated the efficacy and toxicity of the hypomethylating agent decitabine as initial therapy in older patients with AML.

Patients and Methods
In this multicenter, phase II study, patients older than 60 years who had AML (ie, > 20% bone marrow blasts) and no prior therapy for AML were treated with decitabine 20 mg/m^2 intravenously for 5 consecutive days of a 4-week cycle. Response was assessed by weekly CBC and bone marrow biopsy after cycle 2 and after each subsequent cycle. Patients continued to receive decitabine until disease progression or an unacceptable adverse event occurred.

Results
Fifty-five patients (mean age, 74 years) were enrolled and were treated with a median of three cycles (range, one to 25 cycles) of decitabine. The expert-reviewed overall response rate was 25% (complete response rate, 24%). The response rate was consistent across subgroups, including in patients with poor-risk cytogenetics and in those with a history of myelodysplastic syndrome. The overall median survival was 7.7 months, and the 30-day mortality rate was 7%. The most common toxicities were myelosuppression, febrile neutropenia, and fatigue.

Conclusion
Decitabine given in a low-dose, 5-day regimen has activity as upfront therapy in older patients with AML, and it has acceptable toxicity and 30-day mortality.

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INTRODUCTION

The incidence of acute myeloid leukemia (AML) increases with age, but current treatment options for older patients with AML are limited, and their outcomes are poor. Older patients with AML are more likely to have poor-risk cytogenetic abnormalities or a preceding myelodysplastic syndrome (MDS), both of which are associated with lower complete remission (CR) rates. In addition, elderly patients may have comorbid illnesses, poor performance status, or decreased organ function, any of which can impair their ability to tolerate antileukemic therapy. Standard induction chemotherapy with an anthracycline and cytarabine provides a durable remission in a minority of elderly patients considered fit for intensive therapy, at a cost of significant toxicity.[1-3] Consequently, 64% of patients with AML who are older than 65 years are not treated, and their median survival time is only 1.7 months.[4] More effective and less toxic therapies are clearly needed for this patient population.

Correction of aberrant methylation patterns is a promising target in the treatment of hematologic malignancies. Methylation of cytosine in the CpG dinucleotide by DNA methyltransferase leads to transcriptional silencing of genes during normal development, and it has emerged as a significant mechanism for the loss of tumor suppressor gene expression in human cancer, including AML.[5-7] Decitabine (ie, 5-aza-2′-deoxycytidine) is a nucleoside analog that induces hypomethylation of DNA and differentiation of hematopoietic cells.[8,9] Decitabine is incorporated into DNA during S phase and irreversibly inhibits DNA methyltransferase, resulting in loss of methylation and reactivation of silenced genes.[10] Decitabine also has a direct cytotoxic effect at high doses.

Decitabine has been investigated in hematologic malignancies by using a range of doses and schedules. It is currently approved for the treatment

of adults with MDS at a dose of 15 mg/m^2 every 8 hours for 3 days on the basis of a phase III study that demonstrated improved outcomes in patients in the treatment arm compared with patients treated with supportive care alone.[11] Of note, 18% of the patients in the phase III trial had 20% to 30% bone marrow blasts, which met the WHO criteria for AML. Phase I and II studies in AML, which used a variety of low-dose decitabine regimens, have reported overall response rates of 22% to 44%.[12-15] Our study was undertaken to determine the activity of decitabine as first-line therapy for older patients with AML, by using the low-dose schedule of 20 mg/m^2 intravenously (IV) daily for 5 days; this schedule has been studied previously in populations with MDS.[16,17]

PATIENTS AND METHODS

Patient Eligibility

Patients age 60 years or older with a diagnosis of AML and intermediate- or poor-risk cytogenetics[18] were eligible for this study. Patients could have had de novo AML, AML secondary to prior therapy, or transformed from MDS. The diagnosis of AML ($\geq$ 20% bone marrow blasts) was determined by CBC, bone marrow assessment, and immunophenotypic analysis within 2 weeks of study enrollment. Additional inclusion criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; adequate renal and hepatic function; life expectancy greater than 12 weeks; and ineligibility for receipt of standard induction chemotherapy or bone marrow transplantation. Exclusion criteria included the following: prior therapy for AML; diagnosis of acute promyelocytic leukemia; good-risk cytogenetics as defined by Southwest Oncology Group (SWOG) criteria[18]; CNS leukemia; prior therapy with azacytidine; and uncontrolled illness, including active infection.

The study protocol was approved by the Human Research Protection Office at participating institutions. All patients provided written informed consent.

Study Treatment

This was an open-label, single-arm, tricenter, phase II study of low-dose decitabine administered as 20 mg/m^2 IV over 1 hour once daily for 5 consecutive days. Cycles were repeated every 4 weeks. Patients who presented with an absolute peripheral blast count greater than 30,000/μL were treated with hydroxyurea until the absolute blast count was less than 30,000/μL. Decitabine was not administered until the absolute blast count was less than 30,000/μL. Treatment could be delayed at the discretion of the investigator for disease-related complications, such as febrile neutropenia, infection, or hemorrhage, and a 25% dose reduction was allowed for patients who developed treatment-related toxicity. No treatment delay or reduction was required for cytopenias. Patients continued to receive decitabine until one of the following occurred: disease progression, intercurrent illness preventing additional treatment, unacceptable adverse events, patient decision to withdraw from the study, or general or specific changes in the patient condition that made additional treatment unacceptable. Response was assessed by bone marrow aspirates collected after every cycle, beginning with cycle 2. Patients who had a documented CR had bone marrow assessments at the end of the first and third cycles after initial documentation of CR and then as clinically indicated thereafter. Bone marrow aspirates and biopsies were evaluated by local hematopathologists. Response assessments on all patients were centrally determined by two independent external hemato-oncologists on the basis of local bone marrow pathology reports, hematologic laboratory values, and blood/platelet transfusions.

During treatment, CBCs were collected weekly, and serum chemistries were collected every other week. Transfusions and prophylactic antibiotics were administered according to institutional standards. Growth factors were not administered routinely to patients during the study.

Statistical Analysis

All patients were assessed for response according to the International Working Group criteria.[19] The primary end point was morphologic CR.

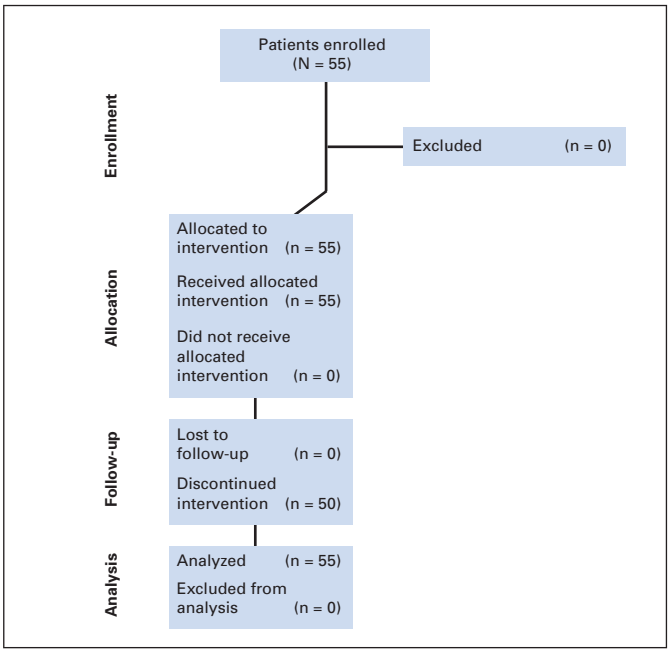

Fig 1. CONSORT diagram.

Secondary end points included cytogenetic CR, morphologic CR with incomplete blood count recovery (CRi), overall survival (OS), event-free survival (EFS; ie, time from first dose to first occurrence of treatment failure, relapse, or death), and relapse-free survival (RFS). The sample size was based on an α level of .05 and a power of .85. Given a target CR rate of 30% and an acceptable CR rate not less than 15%, 54 patients were required. A two-stage design was used, and 39 patients were enrolled in the first stage (CONSORT diagram, Fig 1). If seven or fewer CRs were observed during the first stage, the study would have been stopped. The primary analysis was done by using the intent-to-treat (ITT) population, which was defined as all patients who received at least one dose of decitabine. CR rate was calculated along with the 95% CI. Kaplan-Meier product-limit estimator was used to describe OS, RFS, and EFS. Cumulative incidence of relapse was used to describe remission duration, and death was a competing risk factor. All adverse events were coded by using MedDRA (Medical Dictionary for Regulatory Activities) and were summarized by the investigator with attribution of relationship to study drug and according to National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0.

RESULTS

Patient Characteristics

Fifty-five patients with untreated AML were enrolled on this study (Table 1). The median age of patients was 74 years (range, 61 to 87 years), and there was an even distribution of men and women. It was a generally high-risk group of patients, as 62% of patients were age 70 years or older, and 42% had AML secondary to MDS or prior therapy. Only one of the patients with antecedent MDS had received prior therapy for MDS (ie, lenalidomide). The median baseline BM blast percentage was 50%, and 12 patients (22%) presented with 20% to 30% bone marrow blasts. Baseline cytogenetic findings are detailed in Table 2. Four patients had treatment-related AML that occurred after therapy for breast cancer (n = 3) or non-Hodgkin's lymphoma (n = 1). The median time from diagnosis of AML to first dose of decitabine was 19 days (range, 6 to 257 days). On the central review by

Table 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic	Patients No.	Patients %
No. of patients in ITT	55	
Age, years		
Median	74	
Range	61-87	
60-64	7	13
65-69	14	25
≥ 70	34	62
ECOG performance status		
0	26	47
1	19	35
2	10	18
Cytogenetics		
Intermediate risk	29	53
Poor risk	25	45
Not available	1	2
AML type		
De novo	30	55
Transformed from MDS	19	35
Secondary to prior therapy	4	7
Missing	2	4
Presenting WBC		
Median	2.7	
Range	1-111	
Presenting BM blast %		
Median	50	
Range	0-99	

Abbreviations: ITT, intent-to-treat; ECOG, Eastern Cooperative Oncology Group; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; BM, bone marrow.

Table 3. Response to Treatment in the Intent-to-Treat Population

Variable	No. of Patients	Patients With CR No.	Patients With CR %
Overall	55	13	24
AML diagnosis			
De novo	30	7	23
Transformed from MDS	19	4	21
Secondary to prior therapy	4	2	50
Missing	2	0	
Cytogenetic risk			
Poor	25	6	24
Intermediate	29	6	21
Not available	1	1	
Age, years			
60-64	7	2	29
65-69	14	4	29
≥ 70	34	7	21
Presenting BM blast %			
< 30	18	5	28
30 to < 50	10	2	20
≥ 50	27	7	26
Presenting peripheral blood absolute blast count, cells/μL			
< 1,000	41	12	29
1,000-10,000	11	1	9
> 10,000	3	0	

Abbreviations: CR, complete remission; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; BM, bone marrow.

the independent hemato-oncologists, five patients were deemed to have high-risk MDS rather than AML. None of these five patients was evaluated for response, but all five were included in the denominator for the ITT population.

Treatment With Decitabine

Patients were treated with a median of three cycles of decitabine (range, one to 25 cycles), and 64% of patients received three or more cycles of therapy. Eighty-three (27%) of the total 308 cycles were delayed for a median 11 days (range, 1 to 49 days). Cycles were delayed more often for personal or other reasons (47 cycles in 28 patients) than for hematologic (27 cycles in 16 patients) or nonhematologic (12 cycles in 11 patients) toxicity (> one reason may have been given for dose delay). Dose reductions were uncommon and occurred in only five cycles.

At a minimum follow-up of 1 year, five patients remain on the study treatment, and 50 patients discontinued decitabine because of progressive disease (n = 21), death (n = 11), adverse event (n = 7), investigator decision (n = 6), patient decision (n = 4), or incorrect diagnosis (n = 1). Twelve patients (22%) discontinued study treatment during the first cycle, primarily because of death or progressive disease.

Table 2. Summary of Baseline Cytogenetic Characteristics

Cytogenetic Finding	Patients No.	Patients %
Normal karyotype	20	36.4
+8	6	10.9
abn 11q23*	2	3.6
del(5q)/-5	8	14.5
-7/del(7q)	6	10.9
≥ 3 unrelated abnormalities	6	10.9
Other abnormalities	21	38.2

*The investigators classified both patients with abn 11q23 as poor risk.

Response to Decitabine

According to the AML response criteria,[19] the expert-reviewed overall response rate in the ITT population was 25%; 13 (24%; 95% CI, 13.2% to 37.0%) had morphologic CR, and one (2%) had CRi (Table 3). Of the 34 patients who had a cytogenetic abnormality at baseline, five (15%) achieved a cytogenetic CR. CRs were seen in all subgroups of patients, including in four of 19 patients with a prior history of MDS and in five of 25 patients with poor-risk cytogenetics. The median time from first dose to achieve a CR was 126 days (range, 48 to 238 days), which was equal to 4.5 cycles (Table 4). Of the 14 patients who achieved CR or CRi, six patients (43%) experienced relapse on study. Of note, two of two patients who presented with leukemia cutis exhibited complete resolution of skin lesions and experienced response (ie, CR or CRi).

In addition to the patients who achieved CR or CRi, 16 patients (29%) did not meet criteria for response but maintained stable or

Table 4. Time to Response by Cycle

Cycle	No. of Patients With CR (N = 13)
2	3
3	3
5	3
6	3
9	1

Abbreviation: CR, complete remission.

improved bone marrow blast counts during a median of five cycles of therapy (range, two to 12 cycles). Seventeen patients (31%) were classified as having a treatment failure as a result of early death (n = 9), early withdrawal (n = 6), and/or progressive disease (n = 5). Responses were not assessed for eight patients (15%) by the independent reviewers because of an absence of AML diagnosis (n = 5), lack of a baseline bone marrow evaluation report for the external expert review (n = 1), and/or lack of a bone marrow evaluation after the administration of study drug in the absence of death or disease progression (n = 3).

Survival

The overall median survival in the ITT population was 7.7 months (95% CI, 5.7 to 11.6 months) from the start of decitabine treatment (Fig 2). The median EFS was 5.8 months (range, 3 days to 23.6 months). The Kaplan-Meier estimate of median RFS for patients with a CR was 16.3 months (range, 0.9 to 18.4 months). The median survival for patients who achieved a CR or CRi was 14 months. The 30-day mortality was 7%, and the 6-month survival rate was 60%.

The effects of baseline covariates on time to death were explored in a stepwise Cox proportional hazards regression model, which showed that survival times were longer for women than for men ($P = .048$) and were longer for patients with an ECOG performance status of 0 than for those with an ECOG PS of 2 ($P = .029$). In addition, survival was shorter for patients with higher myeloblast counts at baseline ($P = .023$).

Fifteen patients had antileukemic therapy after experiencing failure with decitabine. Second-line therapies were as follows: another experimental agent (n = 8), standard 7 + 3 induction chemotherapy (n = 4), gemtuzumab ozogamicin (n = 2), and high-dose cytarabine (n = 1). Overall, six patients (11%) were treated with 7 + 3 induction at some point after experiencing failure with decitabine. No patients underwent stem-cell transplantation.

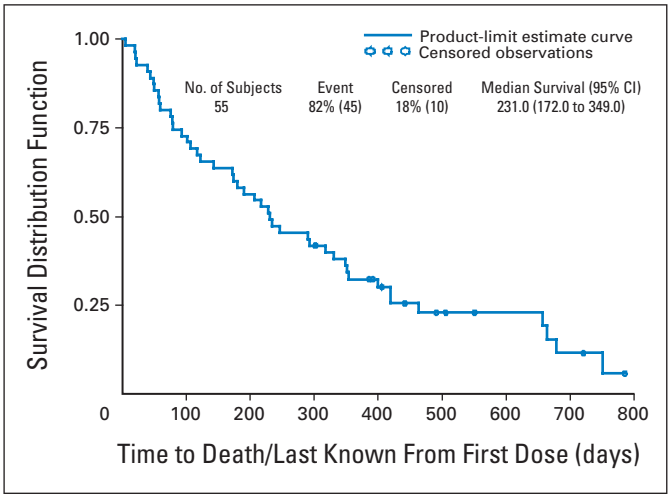

Fig 2. Kaplen-Meier curve for overall survival (intent-to-treat population).

Table 5. Most Frequent Grade 3 or Higher Adverse Events

Event	Patients	
	No.	%
Febrile neutropenia	16	29
Fatigue	14	26
Thrombocytopenia	12	22
Neutropenia	11	20
Anemia	10	18
Dyspnea	8	15
Bacteremia	7	13
Pneumonia	6	11

NOTE. The most frequent events occurred in > 10% of patients.

Toxicity

All patients experienced myelosuppression. The other most commonly reported serious adverse events were febrile neutropenia (29%) and fatigue (26%; Table 5). A total of 26 patients (47.3%) experienced at least one serious adverse event that was considered by the investigator to be related to treatment with decitabine. Related adverse events led to dosing delays in 13 patients (24%) and to dose reduction in one patient (2%). Seven patients (13%) discontinued treatment as a result of an adverse event. Three patients (6%) had at least one adverse event that led to death (sepsis in all three patients).

DISCUSSION

Although the majority of patients diagnosed with AML are older than 60 years of age, older patients with AML often are not candidates for the intensive, potentially curative therapies offered to younger adults. A number of cooperative group trials have enrolled patients with AML who were older than 55 years of age and who were considered fit for multiagent induction chemotherapy; however, the results are generally disappointing, as CR rates have been 50% or less, and substantial toxicity, leading to reported early death rates of 17% to 25%, has occurred.[1,20-22] Median survival of patients treated on these studies ranged from 7.5 to 10 months, which reflected both toxicity and a lack of durable remissions.

Because of the toxicity and uncertain benefit of standard induction chemotherapy in the older population of patients with AML, many of these patients are offered only supportive care or low-intensity chemotherapy. Burnett et al[23] explored this approach in a multicenter trial that randomly assigned more than 200 older patients with AML to low-dose cytarabine or hydroxyurea. The CR rates were 18 versus 1%, respectively; although OS was higher in the low-dose cytarabine arm, the median OS was less than 6 months in both treatment groups. Tilly et al[24] randomly assigned 87 older patients with

AML to low-dose cytarabine or intensive chemotherapy. The patients treated with low-dose cytarabine had a CR rate of 20% and an early death rate of 10%. There was no significant difference in OS between the two groups, and the median OS was 8.8 months in the low-dose cytarabine arm.

Phase I and preliminary phase II studies have demonstrated that decitabine, at a variety of doses and schedules, has activity in AML. In a phase I study that included patients with various hematologic malignancies treated with a range of decitabine doses, the overall response rate in the subset of 37 patients with AML was 22%.[14] Blum et al[13] reported an overall response rate of 44% in patients with untreated or relapsed AML who were treated with decitabine 15 to 20 mg/m^2 daily for 10 days, with or without valproic acid. Lubbert et al[12] conducted a phase II trial of decitabine in untreated, elderly patients with AML, who were in a population similar to that included in this study.[12] They used the dosing regimen studied in the phase III MDS trial: 6-week cycles of decitabine given at 15 mg/m^2 every 8 hours for 3 days, for up to four cycles. All-*trans*-retinoic acid was added in nonresponders, and patients were offered a lower-dose maintenance schedule of decitabine. In 155 evaluable patients, the overall response rate was 25% (CR, 15%), and median OS was 5.5 months.

This multicenter study provides a reliable estimate of the efficacy and tolerability of decitabine as upfront therapy in older patients with AML. The dosing schedule of decitabine chosen for this study was the most active among the low-dose schedules investigated by Kantarjian et al[16] in an MDS population. The patients included were representative of older patients with AML who were not candidates for intensive chemotherapy. The median age was 74 years, and nearly half of the patients had a prior history of MDS or treatment-related AML, which are characteristics that predict a worse outcome. The advanced median age of the study population and the fact that only six patients (11%) subsequently received standard 7 + 3 induction support the concept that this study enrolled patients unlikely to tolerate intensive chemotherapy.

Twenty-four percent of patients in this study achieved a CR, which included complete cytogenetic responses in five of 34 patients. CRs were seen in all patient subgroups, with the exception of the three patients who presented with a peripheral absolute blast count greater than 10,000/μL. In fact, only one (7%) of 14 patients who presented with WBC greater than 1,000/μL achieved a CR. Patients with an absolute blast count greater than 30,000/μL were excluded from this study, and our results confirm that these patients would be unlikely to benefit from decitabine. The median time to CR was 4 months, and the latest CR occurred after cycle 9 (ie, 8 months of therapy), which supports continuing treatment with decitabine at 4-week intervals as long as the patient does not have progressive disease or unacceptable toxicity.

It is worth noting that, in addition to the patients who achieved a CR or CRi, 29% of patients had stable disease for a median of five cycles of therapy. Although stable disease is not a traditionally valuable end point in AML, we did observe patients in this group who had improvement in their disease-related symptoms, peripheral blood counts, and bone marrow blast percentage and who stayed on therapy for many months, despite never meeting the criteria for CR. Only randomized trials will be able to estimate the quality of life or survival benefits in patients who have stable disease on decitabine.

The decitabine dosing schedule used in this study, 20 mg/m^2 daily for 5 days, was well tolerated, and two thirds of patients remained on therapy for three or more cycles. The toxicities observed were primarily infections and cytopenias, as would be expected in an AML population. The 30-day mortality rate of 7% compares favorably with the treatment-related mortality expected when older patients are treated with intensive chemotherapy. It should be noted, however, that mortality at 3 months (after approximately three cycles of decitabine) was 25%, which is similar to that seen in patients older than 60 years of age after induction with conventional chemotherapy.

Fortunately, the treatment landscape is changing for older patients with AML. Clinical trials are exploring novel agents, including laromustine,[25] farnesyl transferase inhibitors,[26] clofarabine,[27] and lenalidomide,[28] in elderly AML, with some promising early results. Allogeneic stem-cell transplantation is becoming an option for more older patients with AML with the use of reduced-intensity conditioning regimens.[29] The conjugated anti-CD33 antibody gemtuzumab ozogamicin is approved for the treatment of elderly patients with relapsed AML, and it has activity as initial therapy as well[30]; however, hematologic and hepatic toxicity can be severe. Additional investigation will be required to define the best use of decitabine, given the available therapies for elderly patients with AML. An ongoing, phase III trial is comparing the outcomes of patients older than 65 years of age who are treated with decitabine, at the schedule used in this study, versus low-dose cytarabine or supportive care. Other dosing schedules of decitabine[31] and combinations of decitabine and histone deacetylase inhibitors are also of interest and are under investigation.

In conclusion, this multicenter, phase II study of first-line treatment of elderly patients with AML on a 5-day schedule of decitabine found a promising response rate with relatively low treatment-related toxicity and mortality. Our results support phase III studies of decitabine in this patient population, to better define decitabine activity and impact on survival compared with standard low-intensity therapies. In addition, future studies should analyze clinical or molecular disease characteristics that may predict response to decitabine to identify those patients most likely to benefit from this therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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