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ORIGINAL REPORT

Phase II Study of Clofarabine Monotherapy in Previously Untreated Older Adults With Acute Myeloid Leukemia and Unfavorable Prognostic Factors

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A B S T R A C T

Purpose
This phase II study assessed clofarabine monotherapy in older adults (≥ 60 years of age) with untreated acute myeloid leukemia (AML) and at least one unfavorable baseline prognostic factor.

Patients and Methods
Clofarabine was administered intravenously for 5 days at 30 mg/m^2/d during induction and 20 mg/m^2/d during reinduction/consolidation (six cycles maximum). The primary end point was overall remission rate (ORR; ie, complete remission [CR] plus CR with incomplete platelet recovery [CRp]).

Results
In 112 evaluable patients who were treated (median age, 71 years; range, 60 to 88 years), the ORR was 46% (38% CR, 8% CRp). ORR by unfavorable prognostic factor was 39% for patients ≥ 70 years of age; 32% for Eastern Cooperative Oncology Group (ECOG) performance status 2; 51% for antecedent hematologic disorder; 54% for intermediate karyotype; 42% for unfavorable karyotype; and 48%, 51%, and 38% for one, two, and three risk factors, respectively. The median disease-free survival was 37 weeks (95% CI, 26 to 56 weeks). Median duration of remission was 56 weeks (95% CI, 33 to not estimable). The estimated median overall survival was 41 weeks (95% CI, 28 to 53 weeks) for all patients, 59 weeks for patients with CR/CRp, and 72 weeks for patients with CR. The 30-day all-cause mortality was 9.8%. The most common non-laboratory drug-related toxicities (≥ 20% patients) were nausea, febrile neutropenia, vomiting, diarrhea, rash, and fatigue.

Conclusion
Clofarabine is an active agent with acceptable toxicity in patients age 60 years or older with untreated AML who have at least one unfavorable prognostic factor. ORR did not seem affected by the presence of multiple unfavorable prognostic factors.

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INTRODUCTION

Conventional induction chemotherapy for acute myeloid leukemia (AML) has consisted of cytarabine plus an anthracycline (7+3 regimen; ie, 7 days of treatment with cytarabine and 3 days of treatment with an anthracycline). Despite modest improvements in outcomes for younger patients with AML, adults older than 55 years (the majority of patients with AML) continue to do poorly.[1] Response rates range from 40% to 55% in patients older than 60 years and from 24% to 33% in patients older than 70 years.[2-5] In patients older than 60 years, response rates range from 26% to 34% with the addition of adverse cytogenetics, 28% to 46% in the presence of antecedent hematologic disorder (AHD), and 26% with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2.[5-10]

The median overall survival (OS) of unselected older adults with AML treated with the 7+3 regimen is 8 to 12 months,[3,5] and less than 10% of patients remain in remission for more than 3 years.[4,11,12] Median OS decreases to 4 to 5 months in older patients with adverse cytogenetics.[5,6]

High induction mortality with the 7+3 regimen contributes to poor survival. Death within 30 days following therapy ranges from 10% to 30% in unselected older adults and rises to 30% to 50% with

increasing age and worsening PS.[6,9,13] Response rates and survival decrease further and mortality rates increase with more risk factors.[13,14] With this risk-benefit profile of the 7+3 regimen, only 30% of older adults in the United States with newly diagnosed AML receive any form of chemotherapy.[15] New therapies are needed to improve outcome in older patients with AML.

The second-generation purine nucleoside analog clofarabine (2-chloro-2′-fluoro-deoxy-9-β-D-arabinofuranosyladenine) was designed to incorporate the favorable qualities of fludarabine and cladribine and to mitigate their often dose-limiting neurotoxicity.[16]

The maximum tolerated dose of clofarabine in adults with relapsed or refractory leukemias was 40 mg/m^2/d intravenously (IV) for 5 consecutive days.[17] Phase II studies evaluated clofarabine 30 mg/m^2/d for 5 days in older adults with untreated AML considered unsuitable for conventional chemotherapy. These studies showed overall remission rates (ORRs) of 44% and 59%, including 42% for patients with adverse cytogenetics and 49% for patients older than 70 years.[18,19] These findings were the basis for this study of single-agent clofarabine in a prospectively well-defined population of older patients with untreated AML and unfavorable baseline prognostic factors.

PATIENTS AND METHODS

Patient Eligibility

The primary objective of this multicenter phase II study was to assess the efficacy of clofarabine in patients ≥ 60 years old with previously untreated AML (de novo, secondary, or with AHD) according to WHO criteria, ECOG PS of 0 to 2, and at least one of four unfavorable prognostic factors consisting of age ≥ 70 years, ECOG PS 2, presence of AHD, or intermediate or unfavorable karyotype.[20] Any cytogenetic profile except for t(8;21)(q22;q22), inv(16)(p13q22) or t(16;16)(p13;q22), or t(15;17)(q22;q12) and variants was eligible. Other eligibility criteria included adequate renal function (serum creatinine ≤ 1 mg/dL or estimated glomerular filtration rate > 60 mL/min),[21] hepatic function (bilirubin ≤ 1.5 × upper limit of normal and AST/ALT ≤ 2.5 × upper limit of normal), and cardiac function (left ventricular ejection fraction ≥ 40% on multigated acquisition scan or echocardiogram). Exclusion criteria included acute promyelocytic leukemia, prior treatment for AML or AHD (except for lenalidomide for AHD), pelvic radiation, clinical evidence of CNS leukemia, uncontrolled infection, or prior hematopoietic stem-cell transplantation (HSCT).

The institutional review board at each site approved the study. Informed consent was obtained according to institutional guidelines. The study was conducted in accordance with the Declaration of Helsinki.

Treatment and Study Design

Clofarabine was supplied by the manufacturer. During induction, clofarabine (Clolar, Genzyme, Cambridge, MA) was administered at 30 mg/m^2 by IV infusion over 1 hour daily for 5 days. Leukemic progression (ie, increase in bone marrow or peripheral blood blast count by ≥ 50% or the appearance of new extramedullary disease) precluded additional clofarabine administration. Patients with residual leukemia who did not meet the criteria for leukemic progression could receive a second treatment cycle (as reinduction) administered after day 28 of cycle 1. Patients with a documented complete remission (CR) or CR with incomplete platelet recovery (CRp) could receive second and subsequent cycles as consolidation. During reinduction or consolidation, the clofarabine dose was 20 mg/m^2 by IV infusion over 1 hour daily for 5 days. A maximum of six cycles was allowed.

Hydroxyurea was allowed up to 24 hours before first dose but not during the study. Supportive measures included prophylactic antibacterial, antifungal, and antiviral agents according to institutional guidelines. Growth factors were not administered prophylactically but were permitted if clinically indicated. Monitoring for and prophylaxis of tumor lysis syndrome were recommended. Daily prophylactic steroids during clofarabine administration were permitted but not mandated.

Adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v3.0). Tolerability of clofarabine was determined by the incidence, severity, duration, causality, seriousness, and type of AEs experienced, including patient deaths.

Prognostic and Response Criteria

Baseline cytogenetic profile was categorized as favorable, intermediate, or unfavorable.[20] The intermediate category was defined as normal (ie, diploid) karyotype. All other cytogenetic abnormalities excluding favorable and intermediate were classified as unfavorable.[20]

CR was defined on the basis of revised International Working Group for Response Criteria[22]: an evaluable bone marrow examination with less than 5% blasts, evidence of normal hematopoiesis, absence of Auer rods, absence of extramedullary disease, no more than rare evidence of circulating blasts (if present, evidence of a regenerating bone marrow was required); and recovery of peripheral blood counts (absolute neutrophil count ≥ 1.0 × 10^9/L and platelets ≥ 100 ×10^9/L without transfusions).[22] Patients meeting all the criteria for CR except for a platelet count ≥ 100 × 10^9/L were categorized as achieving a CRp. All other responses, including partial response, were considered treatment failures.

Efficacy analyses were performed on the intent-to-treat principle and included all enrolled patients with a centrally confirmed diagnosis of AML. Patients were to be followed for at least 2 years after the completion of the treatment period for the last patient enrolled or until death.

A data monitoring committee periodically assessed safety throughout the study, a central pathologist independently confirmed the diagnosis of AML, and an independent response review panel (IRRP) assessed each patient for response and for continued remission and/or disease recurrence in responders.

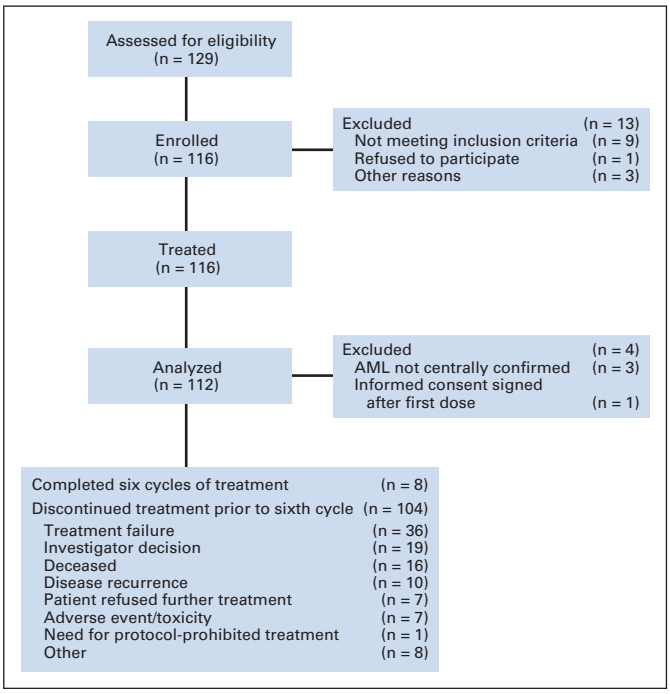

Fig 1. CONSORT diagram. AML, acute myeloid leukemia.

Statistical Analyses

The study utilized the Simon two-stage (minimax) design.[23] The design parameters were as follows: a true response rate in this population of ≤ 18% was considered ineffective (ie, $p_0 = 18\%$), a true response rate of ≥ 30% was considered effective (ie, $p_1 = 30\%$), the false-positive rate (one-sided) was no higher than 5% (ie, $\alpha = .05$), and the false-negative rate was no higher than 10% (ie, $\beta = .10$).

The primary outcome measure was the determination of ORR defined as CR plus CRp. Remission rates were also assessed for the four prospectively defined unfavorable prognostic factors, both singly and in combination. Secondary efficacy end points of duration of remission (DOR), disease-free survival (DFS), and OS were summarized using Kaplan-Meier methodology.[24] DFS was calculated from achievement of CR until disease recurrence or death (the result of any cause), regardless of intervening alternative antileukemic treatment. Patients who initiated alternative antileukemic treatment while in remission (including HSCT) were censored at the time the therapy was initiated for analysis of DOR. For DOR and DFS, patients who were known to be alive without disease recurrence were censored on the date they were last known alive and a bone marrow examination confirmed ongoing remission. OS was calculated from first dose of clofarabine to death.

Table 1. Patient Baseline Characteristics (N = 112)

Characteristic	No. of Patients	%
Age, years		
Median	71	
Range	60-88	
≥ 70	69	62
< 70	43	38
Female	60	54
Race		
White	98	88
Black or African American	7	6
Asian	4	4
Ethnicity		
Hispanic or Latino	4	4
ECOG performance status		
0	21	19
1	66	59
2	25	22
Presence of AHD	41	37
Prior MDS	32	29
Prior MPD	9	8
Secondary AML*	11	10
Karyotype		
Unfavorable	62	55
Intermediate	46	41
Not reported	4	4
No. of baseline unfavorable prognostic factors†		
1‡	25	22
2	45	40
3	40	36
4	2	2
White blood cell count (10^9/L)		
> 50	7	6
≤ 50	105	94
Blast %		
Bone marrow, median	51	
Peripheral blood, median	15	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; AHD, antecedent hematologic disorder; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; AML, acute myeloid leukemia.

*Secondary AML is AML in a patient with a history of prior chemotherapy or radiation therapy.

†Baseline unfavorable prognostic factors: age ≥ 70 years, ECOG performance status 2, AHD, and intermediate/unfavorable karyotype.

‡Seven (6%) patients had intermediate karyotype as the only baseline risk factor.

Table 2. Best Response Assessed by IRRP (N = 112)

Response	No. of Patients	%	95% CI
ORR (CR + CRp)	51	46	36 to 55
CR	42	38	29 to 47
CRp	9	8	ND

Abbreviations: IRRP, independent response review panel; ORR, overall response rate; CR, complete remission; CRp, CR with incomplete platelet recovery; ND, not determined.

Table 3. IRRP-Assessed Overall Remission Rates by Baseline Prognostic Factor

Baseline Prognostic Factor	Total No. of Patients	No. of Patients CR + CRp	%	95% CI
Age, years				
< 70	43	24	56	40 to 71
≥ 70	69	27	39	28 to 52
ECOG performance status				
0-1	87	43	49	39 to 60
0	21	14	67	ND
1	66	29	44	ND
2	25	8	32	15 to 54
Presence of AHD				
Yes	41	21	51	35 to 67
Prior MDS	32	20	63	ND
Prior MPD	9	1	11	ND
No	67	29	43	31 to 56
Not reported	4	1	25	ND
Secondary AML*	11	5	45	ND
Cytogenetics				
Intermediate	46	25	54	39 to 69
Unfavorable	62	26	42	30 to 55
Not reported	4	0	0	ND
No. of risk factors†				
1	25	12	48	ND
2	45	23	51	ND
3	40	15	38	ND
4	2	1	50	ND
Blast karyotype				
Complex (≥ 3)	27	9	33	ND
Chromosome 7 abnormal	19	6	32	ND
Chromosome 5 abnormal	16	3	19	ND
+8	18	11	61	ND
Other abnormalities	44	16	36	ND

Abbreviations: IRRP, independent response review panel; CR, complete remission; CRp, CR with incomplete platelet recovery; ECOG, Eastern Cooperative Oncology Group; ND, not determined; AHD, antecedent hematologic disorder; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; AML, acute myeloid leukemia.

*Secondary AML, AML in patient with a history of prior chemotherapy or radiation therapy.

†Defined at baseline as ≥ 70 years old, ECOG performance status 2, AHD, or intermediate/unfavorable karyotype.

RESULTS

Patient Characteristics

Of 116 patients enrolled at 20 US sites, 112 were included in the analyses (Fig. 1). Three patients were excluded because the AML diagnosis was not centrally confirmed, and one patient was excluded because signed informed consent was not provided before treatment. The median age at enrollment was age 71 years (range, 60 to 88 years). The patient baseline characteristics are detailed in Table 1. The median bone marrow blast count was 51%.

When assessed by prespecified unfavorable prognostic factors, 62% of patients were ≥ 70 years old, 22% had an ECOG PS of 2, 37% had AHD, 41% had intermediate cytogenetics, and 55% had unfavorable cytogenetics. The majority of patients (78%) had at least two unfavorable prognostic factors. Since only seven (6%) patients had intermediate cytogenetics as their only unfavorable prognostic factor, this subgroup was not further analyzed individually.

The median number of clofarabine cycles was two (range, one to six). Eight patients (7%) received six cycles of treatment. All 112 patients received the first induction cycle; 66 (59%) patients initiated a second cycle of clofarabine, 38 as reinduction and 28 as consolidation. The median number of consolidation cycles was one (range, zero to five cycles) for the 38 cycle 1 responders and zero (range, zero to four cycles) for the 13 cycle 2 responders. The median time between cycles 1 and 2 (either as reinduction or consolidation) was 41 days (range, 23 to 83 days), and the median time between cycles 2 and 3 was 39 days (range, 23 to 63 days).

Response As Assessed by IRRP

The ORR was 46% including 38% CRs (Table 2). Of the 51 patients in remission, 38 (75%) achieved a CR or CRp after the first induction cycle and 13 (25%) achieved remission after the reinduction cycle. The median time to remission was 5 weeks (range, 3 to 20 weeks). The median time to peripheral blood blast clearance was 5 days (95% CI, 5 to 13 days).

The ORR for the prespecified risk groups was as follows (Table 3): 39% for age ≥ 70 years, 32% for ECOG PS 2, 51% for AHD, 54% for intermediate cytogenetics, and 42% for unfavorable cytogenetics. The ORR by the number of unfavorable risk factors was 48% for one risk factor, 51% for two, and 38% for three. ORR among patients with complex karyotype (≥ three abnormalities), abnormalities of chromosome 7, and abnormalities of chromosome 5 was 33% (9 of 27), 32% (6 of 19), and 19% (3 of 16), respectively. The ORR was 56% in patients age 60 to 69 years and 67% in patients with PS 0.

DFS, Duration of Response, and OS by IRRP

The median duration of follow-up from first dose for all patients was 36 weeks (range, 1 to 85 weeks). The median DFS was 37 weeks (95% CI, 26 to 56 weeks; Fig 2A). The median DOR, censoring for alternative treatment, was 56 weeks (95% CI, 33 to not estimable). No statistically significant differences were seen in DFS or DOR among the four baseline unfavorable prognostic factor subgroups (data not shown). Five of 51 patients in remission (four CR, one CRp) proceeded to HSCT. Fourteen additional patients in remission, as assessed by the IRRP, proceeded to alternative therapy while in

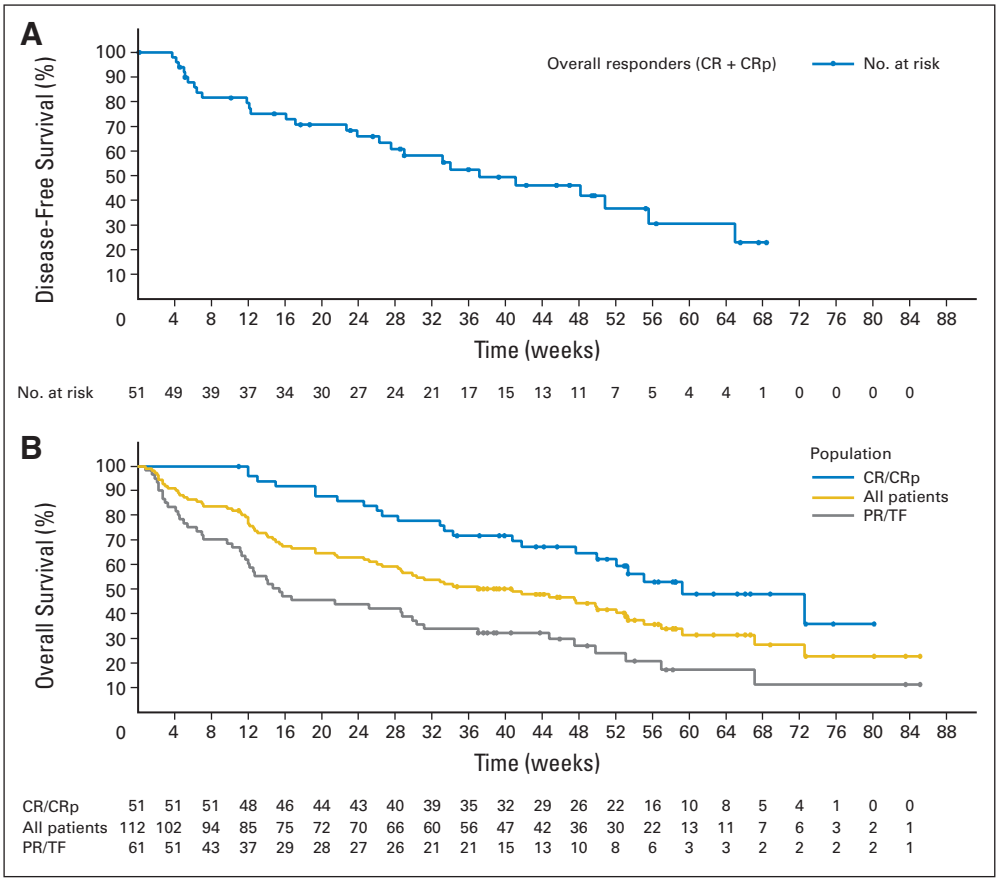

Fig 2. (A) Kaplan-Meier estimate for disease-free survival (DFS). The median DFS was 37 weeks (95% CI, 26 to 56 weeks). (B) Kaplan-Meier estimates for overall survival (OS) of all patients, patients with complete remission (CR) or complete remission with incomplete platelet recovery (CRp), and patients with partial response (PR) or treatment failure (TF). Median OS was 41 weeks (95% CI, 28 to 53 weeks) for all patients, 59 weeks (95% CI, 50 to not estimable) for patients who achieved CR or CRp, and 15 weeks (95% CI, 12 to 30 weeks) for patients with PR or TF.

remission. Median OS was 41 weeks (95% CI, 28 to 53 weeks) for all patients, 59 weeks for patients who achieved CR or CRp, and 72 weeks for patients who achieved a CR (Fig 2B). To mitigate the impact of survivorship bias, landmark analyses (including only patients who survived until the landmark time point) were performed using time points of 30, 45, and 60 days; ORR and CR were statistically significant predictors of residual survival regardless of time point (all $P < .05$). Patients continue to remain in long-term follow-up, with 42 alive at the most recent data cutoff (November 2008).

Tolerability

The majority of patients (96%) experienced an AE considered related to clofarabine, but only seven patients (6%) discontinued treatment because of an AE, including prolonged myelosuppression, thrombocytopenia, acute myocardial infarction (in two patients), acute respiratory distress syndrome, amnesia, and renal failure.

The all-cause 30-day mortality rate was 9.8%, and the all-cause 60-day mortality rate was 16%. Thirty-day mortality was 13% (9 of 69) among patients ≥ 70 years old, 9% (1 of 11) among patients ≥ 80 years old, and 12% (3 of 25) among patients with PS 2.

Table 4 presents all drug-related, non-laboratory AEs reported in more than 10% of patients. The most common drug-related, non-laboratory AEs in ≥ 20% of patients were nausea, febrile neutropenia, vomiting, diarrhea, rash, and fatigue. Febrile neutropenia was the most common grade ≥ 3 AE. During the first induction cycle, 21% of patients received myeloid growth factors.

Either febrile neutropenia or fever (regardless of causality) occurred in 102 (91%) patients at any time on therapy. There were no reports of systemic inflammatory response syndrome or hepatic veno-occlusive disease, and only one patient had grade 1 palmar-plantar erythrodysesthesia. One patient developed a grade 2 nonserious capillary leak syndrome that resolved. Mild to moderate pancreatitis was reported in six patients (three were considered related to clofarabine, including two grade 1 and one grade 2). Drug-related mucositis of any grade occurred in only 21% of patients and grade 3 or 4 in 3% and 0%, respectively.

Table 4. Drug-Related Non-Laboratory Adverse Events Reported in > 10% of Patients (N = 112)

Adverse Event	All Grades		No. of Patients at Maximum NCI CTCAE Grade		
	No. of Patients	%	3	4	5
Any treatment-related adverse event	108	96	50	27	4
Nausea	70	63	4	0	0
Febrile neutropenia	45	40	42	3	0
Vomiting	45	40	0	0	0
Diarrhea	38	34	2	0	0
Rash	33	30	2	0	0
Fatigue	22	20	3	0	0
Headache	17	15	0	0	0
Pyrexia	16	14	2	0	0
Anorexia	15	13	3	0	0
Mucositis*	24	21	3	0	0
Pruritus	13	12	1	0	0

Abbreviations: NCI, National Cancer Institute; CTCAE, Common Terminology Criteria for Adverse Events.
*Inclusive of mucosal inflammation, stomatitis, mouth ulceration, and aphthous stomatitis.

Table 5. Grade 3/4 Treatment-Emergent Hematologic, Hepatic, Renal, and Pancreatic Laboratory Changes (N = 112)

Laboratory Parameter	Any Grade		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Anemia	68	61	44	39	4	4
Neutropenia	58	52	5	5	52	46
Thrombocytopenia	85	76	4	4	77	69
Elevated total bilirubin	60	54	12	11	0	0
Elevated AST	86	77	23	21	3	3
Elevated ALT	92	82	20	18	1	1
Elevated creatinine	40	36	7	6	0	0
Elevated amylase	20	18	6	5	0	0
Elevated lipase	32	29	9	8	6	5

The median times to neutrophil recovery for all cycles (patients with CR or CRp) to ≥ 0.5×10^9/L and ≥ 1×10^9/L were 26 days (range, 11 to 35 days) and 28 days (range, 11 to 57 days), respectively. The median times to platelet recovery (patients with CR) to ≥ 50×10^9/L and ≥ 100×10^9/L were 24 days (range, 12 to 65 days) and 26 days (range, 16 to 65 days), respectively.

Table 5 presents grade 3/4 treatment-emergent hematologic, hepatic, renal, and pancreatic laboratory changes. Transient grade 3 or 4 AST or ALT elevations occurred frequently but returned to grade ≤ 2 in a median of 4 and 6 days and to baseline in a median of 9 and 15 days, respectively. Twelve patients had bilirubin elevations of grade ≥ 3, and eight patients recovered to grade 2 or lower in a median of 5 days and to baseline in a median of 8 days. Four patients had grade 3 elevations in serum bilirubin at the last time point measured and died from unrelated causes. Grade 3 elevations in serum creatinine were seen in seven patients, all in the setting of other serious AEs such as sepsis and hypotension.

DISCUSSION

The results of this multicenter, phase II study indicate that single-agent clofarabine is active and well tolerated in older adults with untreated AML and unfavorable prognostic factors. The ORR in this study was 46% (38% CR), with the majority of the responses occurring after cycle 1. When analyzed by subgroups, ORR was 39% for patients ≥ 70 years, 32% with ECOG PS 2, 51% with AHD, and 42% with unfavorable cytogenetics.

In contrast to earlier studies of intensive chemotherapy in this population,[13,14] ORR after clofarabine was not affected by the presence of multiple adverse prognostic factors (48%, 51%, and 38% in patients with one, two, or three risk factors, respectively).

The clinical benefit of the ORR in this study is supported by two measures of remission durability, DFS and DOR. Censoring of DOR for patients who initiated alternative therapy while in remission accounts for the differences in median DFS and DOR, although the 95% CIs for DOR and DFS overlap. A number of these DOR-censored patients experienced events (ie, relapse or death) after initiating alternative therapy, thus reducing the median for DFS relative to that for DOR.

The median DFS and DOR of ≥ 37 weeks with single-agent clofarabine compares favorably with outcomes with 7+3 induction therapy in older patients with AML. One study reported a median DFS of 10 to 11 months in selected patients age 60 years or older with no AHD who received postremission intensification therapy.[25] However, DFS was only 9 months for patients without core binding factor or normal cytogenetics.[25] Other studies in unselected older AML patients treated with the 7+3 regimen reported a median DFS of 7 to 11 months for patients age 56 years or older.[4,5,26] Outcomes in the subset of patients with at least one unfavorable prognostic factor, as defined in this study, would be expected to be worse. The median OS in this study was 41 weeks, which is similar to results from other studies in unselected older patients with AML.[1-3,5,6]

The all-cause 30-day mortality of 9.8% observed in this study compares favorably with that in studies with similar patient populations treated with the 7+3 regimen. In three large cooperative group studies of older patients with AML that did not require the presence of unfavorable prognostic factors and included younger patients (ie, age 55 to 60 years), the 30-day all-cause mortality ranged from 15% to 26%.[4,5,27] In a retrospective analysis of five trials of 968 adult patients with newly diagnosed AML,[6] the 30-day all-cause mortality for patients age 66 years or older with baseline PS 0 to 2 ranged from 12% to 50%. Although the patient numbers were small (n = 25), the 30-day mortality in our study for patients with PS 2 was only 12%. In a retrospective study of 998 older patients (age ≥ 65 years) with AML treated with conventional chemotherapy,[13] the 60-day mortality ranged from 27% to ≥ 60%, depending on the presence of one to three unfavorable factors. In comparison, the 60-day mortality in our study was only 16%.

AEs in this study were consistent with those seen with 7+3 induction therapy; drug-related toxicities were also consistent with those in prior studies of single-agent clofarabine. In contrast to the 7+3 regimen, which has a 36% reported incidence of mucositis/stomatitis,[28] the incidences of these toxicities were low following clofarabine treatment.

Intensive cytotoxic chemotherapy (7+3) for older adults with newly diagnosed AML is inadequate for a substantial number of patients because of patient- and disease-related factors, which lead to inferior remission outcomes and increased early mortality. Several lower-intensity or targeted therapies have been evaluated as induction therapy in older patients with AML. In a randomized study of low-dose cytarabine versus hydroxyurea in 217 patients,[29] low-dose cytarabine had a better CR rate (18% *v* 1%; $P < .00006$) and longer survival ($P = .0009$). Only 15% to 25% of patients treated with decitabine achieved CR in two phase II trials.[30,31] Response with decitabine can be delayed by several months, and outcomes were worse in patients with high baseline WBC counts. In several phase II studies, gemtuzumab ozogamicin demonstrated low ORRs (17.5% to 25%), but considerable treatment-related mortality was still present.[32,33] Laromustine therapy in older patients with AML without AHD showed an ORR of 37%, CR rate of 29%, and induction mortality of 14%.[34] Other ongoing studies for older adults with AML are evaluating azacitidine,[35] voreloxin,[36] CPX-351,[37] and arsenic trioxide plus low-dose cytarabine.[38]

In summary, the results from this study show that clofarabine is an effective agent with acceptable toxicity and low mortality in older patients with one or more unfavorable prognostic factors. A randomized trial will soon begin enrollment at ECOG comparing clofarabine to the 7+3 regimen as initial therapy for older patients with AML. Further investigation of clofarabine in combination with conventional and novel agents is currently ongoing.

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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