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Low-dose decitabine for previously untreated acute myeloid leukemia ineligible for intensive chemotherapy aged 65 years or older: a prospective study based on comprehensive geriatric assessment

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Abstract

Background: The outcome of patients with acute myeloid leukemia (AML) aged ⩾65 years is poor. Effective treatment options are limited for patients with AML who cannot tolerate intensive chemotherapy.

Objectives: We aimed to evaluate the efficacy of low-dose decitabine in previously untreated patients with AML aged ⩾65 years who were ineligible for intensive chemotherapy based on a comprehensive geriatric assessment.

Design: We performed a prospective, multicenter, open-label, and non-randomized study.

Methods: Patients were enrolled at four centers in Beijing between 1 January 2017 and 31 December 2020. They were treated with decitabine at a dose of 6 mg/m^2 for 10 days. The treatment was repeated every 28 days for one cycle for a total of six cycles. The primary endpoint of our study was overall survival (OS) at the end of the first year after enrolment. The secondary endpoints included overall response rate, leukemia-free survival, relapse rate, treatment-related mortality (TRM), quality of life, safety, and transfusion dependence. Patients were continuously monitored for toxicity.

Results: Overall, 47 patients (30 males and 17 females) participated in this study. The median age of the enrolled patients was 78 (range, 65–90) years. The median follow-up time was 22.2 (range, 4.6–38.8) months. Fifteen (31.9%) patients achieved complete remission (CR), 11 (23.4%) patients achieved partial remission, 3 (6.4%) patients achieved hematological improvement only, and 18 (38.3%) patients did not achieve remission. The median time to obtain CR was 2 months. The median CR was 8.5 months. Of the patients, 36 (76.6%) patients completed six cycles of treatment with low-dose decitabine, and the 1-year OS was 36.1%. According to instrumental activities of daily living scales, age, comorbidities, and albumin (IACA) scores, the median survival was 11.2 months in the unfit group and 6 months in the frail group. The 1-year OS rates in the unfit and frail groups were 49.2% and 23.4%, respectively. Grade ⩾3 non-hematological toxicity was observed in 70.2% (33/47) of the patients. TRM occurred in three patients. No early deaths occurred after treatment.

Conclusion: In newly diagnosed older patients with AML whose IACA assessment was unfit or frail for standard chemotherapy, treatment with low-dose decitabine demonstrated clinical activity and good security in our study.

Keywords: AML, comprehensive geriatric assessment, elderly, low-dose decitabine, treatment

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Introduction

The survival of older patients with acute myeloid leukemia (AML) is significantly worse than that of younger patients with AML. This is attributed to the lower tolerance to intensive treatment and higher rates of poor cytogenetic and/or molecular abnormalities in the older population.[1–4]

In elderly patients, the standard treatment options include intensive chemotherapy, lower-intensity treatment, and best supportive care. The choice of treatment for elderly patients with newly diagnosed AML depends on their fitness and willingness to undergo treatment. However, no consensus regarding the treatment scheme for AML in patients aged >60 years has been established. In our previous study, instrumental activities of daily living (IADL) scales, age, comorbidities, and albumin (IACA) index have been identified to predict clinical outcomes in elderly patients with AML.[5] We verified that the IACA index is a concise and effective assessment tool for elderly patients with AML. The parameters of the IACA index include age, functional status (using the IADL scale), nutritional status (serum albumin), and comorbidity [Charlson Comorbidity Index (CCI) score].[5,6]

Complete remission (CR) rates of intensive chemotherapy in selected older patients with AML were 40–50%, and the early mortality rates were 20–40%.[7–10] The median survival time was only 6–9 months, and the 2-year survival rate was <20%. Hypomethylating agents (HMAs), such as 5-azacitidine and decitabine, have been used in patients with AML who are ineligible for intensive induction chemotherapy. HMAs have modest benefits in patients with AML. The remission rate was approximately 17–25%, and the median overall survival (OS) was approximately 9 months as previously reported.[11–16] Azacitidine added to venetoclax demonstrated promising efficacy,[17,18] with a combined incidence of CR and CR with incomplete hematologic recovery of 66.4–71% and a median OS of 14.7–16.9 months. However, patients in China will not be able to obtain venetoclax in pharmacies until 2021. Moreover, the price of venetoclax remained relatively high after its listing, and not all patients could afford it.

Decitabine is a typically used HMA to inhibit DNA methyltransferases. It was first used to treat high-risk myelodysplastic syndrome (MDS), and its therapeutic efficacy has been reported.[19,20] Decitabine has also been investigated for use in AML treatment in certain situations. It is often used to treat elderly patients with AML who are not candidates for intensive chemotherapy.[21] CR and CRi with previously reported standard doses of decitabine were approximately 20–30%.[22] A randomized trial comparing decitabine (20 mg/m^2 daily for 5 days administered every 4 weeks) *versus* low-dose cytarabine or supportive care in older patients with AML showed a small improvement in survival in patients treated with decitabine in an unplanned analysis.[23] In a study by Lubbert *et al.*,[15] decitabine was administered to elderly medically unfit patients with AML. In their study, the median OS was 5.5 months, and the 1-year OS rate was 28%. Decitabine was well-tolerated by all patients. The reported remission rate has been higher in the decitabine group than in the best-supported treatment group,[14] and decitabine therapy may also be associated with survival rates similar to those of intensive chemotherapy in elderly patients with AML.[24] A previous study has reported a 2-year OS rate of 25% in the decitabine group.[14]

In our practice of decitabine treatment, some elderly patients with AML who received a standard-dose of decitabine experienced a long period of bone marrow suppression or were easily infected. Regular treatment often gets delayed in these patients because of infection or bone marrow suppression. In our previous study, some patients received low-dose decitabine (6 mg/m^2/day for 10 days). The safety and effectiveness were preliminarily verified. The 1-year OS of this small group of patients was 25% (>10%), as reported in the supportive treatment literature.[5,6]

The predictive value of the IACA index for effectiveness in elderly patients with AML has been previously published.[5] Herein, we report the efficacy and safety of low-dose decitabine in previously untreated elderly patients with AML who were ineligible for intensive chemotherapy according to the IACA index.

Methods

Study design and patients

This was a prospective, multicenter, open-label, non-randomized study. Patients with AML were screened at each center. The patients were enrolled at four medical centers in China between

1 January 2017 and 31 December 2020. Eligible patients aged ⩾65 years, with previously untreated AML according to the World Health Organization diagnostic criteria, were categorized as the unfit group or frail group according to the IACA assessment.[25]

The key exclusion criteria were central nervous system AML involvement, other malignancies diagnosed or treated within 1 year before admission to the study, major organ dysfunction, or active infection. Patients with acute promyelocytic leukemia were excluded from the study. Patients with a history of hematological disorders were included if they had not previously been treated with chemotherapy or HMAs. Patients with therapy-related myeloid neoplasms were also included if they did not receive any treatment for the primary malignancy in the preceding 12 months.

Written informed consent was obtained from all the enrolled patients. All eligible patients who met the inclusion criteria and voluntarily signed an informed consent form were screened for inclusion. Response and safety analyses were performed in the intention-to-treat population. None of the patients were excluded after enrolment in the study. Treatment toxicities were assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, for adverse events (AEs).[26,27] Cytogenetic and molecular classifications were based on the National Comprehensive Cancer Network Criteria 2021.

Definitions

OS was defined as the time from the beginning of treatment to the date of all-cause mortality or last follow-up. Early mortality was evaluated 30 days after treatment. Treatment-related mortality (TRM) was defined as death without evidence of leukemia relapse or progression.

The responses were defined according to the Response Assessment of the Modified International Working Group guidelines for AML.[28] CR was defined as a morphological CR that requires the patient to achieve the morphologic leukemia-free state and have an absolute neutrophil count of $>1.0 \times 10^9$/L and platelets of 100×10^9/L. The patient must also be transfusion-independent. The morphologic leukemia-free state requires <5% blasts in the bone marrow aspirate sample, with a count of at least 200 nucleated cells. There should be no blasts with Auer rods or persistent extra-medullary disease.[28] CR with incomplete blood count recovery (CRi) was defined as a condition that met all criteria for CR, except for residual neutropenia ($<1 \times 10^9$/L) or thrombocytopenia ($<100 \times 10^9$/L). Partial remission (PR) requires a decrease in the percentage of blasts in the bone marrow by at least 50%. The treatment failure category included patients in whom treatment efficacy was lower than that of PR. Relapse after CR was defined as the reappearance of leukemic cells in the peripheral blood or >5% blasts in the bone marrow. The overall response rate (ORR) was defined as CR, CRi, and PR according to the modified International Working Group criteria.[28] Hematological improvement (HI) was defined as an improvement in at least one of the hemoglobin, platelet, and neutrophil levels maintained for ⩾6 months. Stable disease (SD) was defined as the absence of CR, CRi, PR, and HI but without evidence of progressive disease after treatment. Non-responders were defined as patients who did not achieve CR, CRi, PR, HI, or SD. Progression-free survival (PFS) was measured from the time of the first dose to disease progression or death from any cause. Patients who did not experience disease progression or death were censored on the day of the last follow-up for the PFS analysis.

IACA index

The IACA index consists of four elements: IADL scales, age, serum albumin level, and burden of clinical comorbidities (assessed using the CCI score). The scoring criteria are presented in the attachment (Supplemental Table 1). According to the IACA index score, patients who were categorized as the unfit group (1–2 points) or frail group (⩾3 points) were enrolled in our study.[5,25,29] The CCI score was assigned by a specially assigned person to evaluate comorbidities during diagnosis.[30] Special staff members also evaluated the ability of patients to perform activities of daily living using the IADL scale.[5,31]

Treatment regimens

The patients were treated with decitabine at a dose of 6 mg/m^2 for 10 consecutive days in 28-day cycles for a total of six cycles, regardless of achieving a response. Bone marrow evaluation was performed using morphological and

immunophenotyping analyses after the second cycle and was repeated after each cycle to assess the response. All patients in our study underwent blood routine tests weekly and after the first course, bone marrow aspiration was performed if necessary. We collected data on the treatment process, survival, and AEs for all patients throughout the treatment period.

Subsequently, patients who achieved CR or CRi were treated with ongoing maintenance cycles of low-dose decitabine every 1–3 months. Patients who did not achieve CR or CRi could continue treatment with decitabine monthly at the discretion of the investigators or they might turn to other treatments, such as the best supportive treatment or clinical trial. Decitabine was continued until disease progression, death, or withdrawal of informed consent from the patients or doctors for any cause.

Evaluation

The primary endpoint of our study was the OS rate at the end of the first year of enrolment in the study. The secondary endpoints were ORR, leukemia-free survival, relapse rate, TRM, quality of life, safety, and transfusion dependence. Patients were continuously monitored for toxicity. Safety was assessed with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[26,27]

Statistical analysis

The sample size was calculated based on the precision of the estimated 1-year OS and the power of the primary endpoint compared to historical data. According to a previous study,[32] the 1-year OS of the best supportive treatment group was 10%, and the 1-year OS of the decitabine group is expected to increase to 25%. Using a binomial exact test, the power was >0.90, demonstrating statistical significance at the two-sided α level of 0.05. All the patients with AML who had received at least two cycles of decitabine were analyzed for their primary response to treatment and the safety of therapy. The ORRs are summarized as the percentage of responders with 95% confidence intervals (CIs). The OS of 1-year or 2-year was estimated using the Kaplan–Meier method with a corresponding 95% CI. PFS was estimated using the reverse Kaplan–Meier method.

Statistical analyses were performed using the IBM SPSS Statistics version 23 for Windows (IBM Corp., Armonk, NY, USA). Categorical variables were analyzed using the chi-squared test or Fisher's exact test. Continuous variables were analyzed using Student's *t*-test. Survival was analyzed using the Kaplan–Meier method and compared using the log-rank test. All p values were two-sided, and statistical significance was set at $p < 0.05$.

The reporting of this study conformed to the Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) 15 September 2015.[33] The study flowchart and the checklist are available in Supplemental Material.

Results

Patient characteristics

Between 1 January 2017 and 31 December 2020, a total of 149 patients were screened, and 47 newly diagnosed patients (23 patients with AML without a history of MDS and 24 with a history of MDS) aged $\geqslant$65 years who underwent the comprehensive geriatric assessment (CGA) and met the inclusion criteria from four centers in China were enrolled in this study for further analysis (Figure 1). The detailed baseline characteristics are listed in Table 1. Of the patients, 34 (72.3%) patients were aged >75 years, 30 patients (63.8%) were male, and 17 patients (36.2%) had poor-risk cytogenetics (i.e. −5, −7, mono-karyotype, or complex karyotype).

The median time from AML diagnosis to decitabine initiation was 41 days [interquartile range (IQR), 28–66 days]. During the period between diagnosis and treatment with decitabine, symptomatic, anti-infective, and supportive treatments required by the disease were administered as required. The patients received a median of four completed cycles (IQR, 2–6); only 17 (36.2%) patients completed six cycles. No significant differences in the median time from diagnosis to decitabine initiation were observed in the 17 patients who completed six cycles and all patients included in this study.

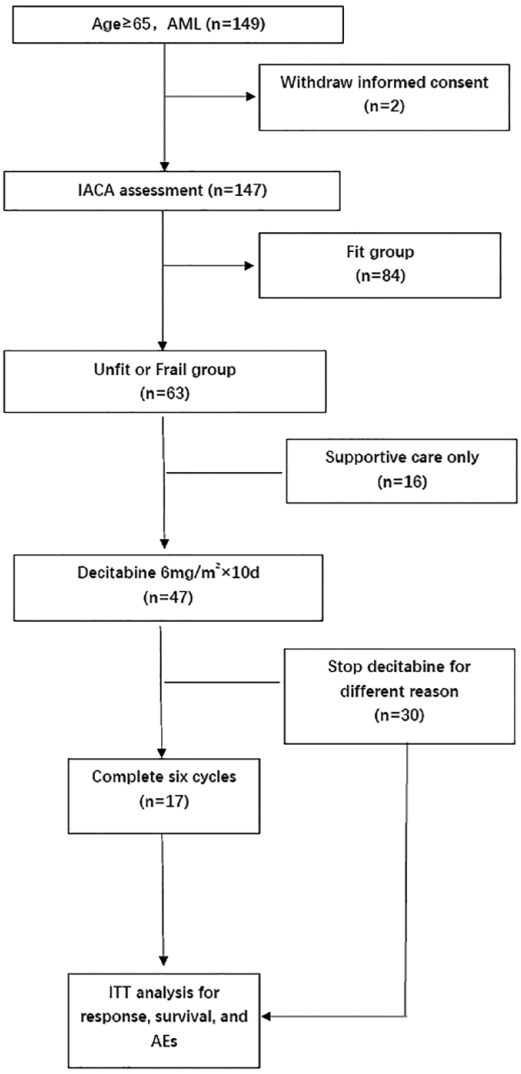

Figure 1. Trial profile.

The baseline mutational profile of commonly mutated genes in AML was determined in 35 patients (74.5%). The incidence of mutations, response rates, and survival rates in the study population are summarized in Table 2. *ASXL1* was the most frequently mutated gene (9/35, 25.7%) in these tested patients, followed by *TET2* (7/35, 20.0%), *NPM1* (7/35, 20.0%), *DNMT3A* (6/35, 17.1%), *FLT3* (6/35, 17.1%), and *TP53* (6/35, 17.1%) (Table 2).

Response

At the end of the follow-up period (31 August 2021), the median follow-up was 22.2 months (range, 4.6–38.8 months). The median number of completed decitabine cycles was four (range, 1–10). Response rates are presented in Table 3. The CR + CRi and PR rates were 31.9% and 23.4%, respectively. Two patients achieved HI without objective response. The clinical benefit rate (CR + CRi + PR + HI only) was 61.7% (29/47). The median time to the best response to CR or CRi was two cycles (range, 1–6 cycles), and the median duration of CR was 8.9 months (range, 2.5–36.3 months).

Regarding the response to different genetic abnormalities, the highest rates of CR and CRi responses were observed in patients with mutations in *EVI1* (33.3%). The lowest CR or CRi response rates were observed in patients with *FLT3*, *TP53*, *RUNX1*, and *IDH1*/*IDH2* mutations (Table 2).

As for subsequent therapy, 20 patients continued to use decitabine, 19 patients turned to best supportive care or observation, 6 patients turned to azacitidine, 1 patient was treated with azacitidine plus venetoclax, and 1 patient with the *FLT3-ITD* mutation was treated with sorafenib. The patient treated with sorafenib did not exhibit any response and died of the infection. The patient treated with azacitidine plus venetoclax achieved CR for 8 months and relapsed. Of the patients using azacitidine, one had CR, one had PR, and four had NR.

Overall survival

With a median follow-up of 22.2 (4.6–38.8) months, the median OS was 9.4 (95% CI, 5.9–12.8) months. The 1-year and 2-year OS rates were 36.1% and 15.9%, respectively (Figure 2(a)). The median OS among patients with AML without a history of MDS was 7.4 months (95% CI, 4.9–9.8), and the median OS among patients with AML with a history of MDS was 13.9 months (95% CI, 7.4–20.5). No significant difference in OS was observed between AML patients with and without a history of MDS ($p = 0.085$) (Figure 2(b)).

Among patients with intermediate or favorable cytogenetic alterations, the median OS was 9.9 months (95% CI, 7.5–12.2), whereas in those with poor cytogenetic alterations, the median OS was 7.0 months (95% CI, 5.5–8.5). No

Table 1. Patient demographics and baseline characteristics.

Characteristic	Total (*N* = 47)	AML without MDS history (*N* = 23)	AML with MDS history (*N* = 24)
Age at diagnosis (years)	78 [73.5, 81]	78 [75.5, 81]	77 [72, 81.3]
Age, ⩾75 years	34 (72.3)	18 (78.3)	16 (66.7)
Gender			
Male	30 (63.8)	15 (65.2)	15 (62.5)
Female	17 (36.2)	8 (34.8)	9 (37.5)
WBC ($\times 10^9$/L)	4.4 [2.3, 18.0]	6.3 [2.4, 34.7]	3.6 [2.3, 7.7]
Hemoglobin (g/L)	81 [62, 96]	87 [65, 98]	75 [59, 87]
Platelets ($\times 10^9$/L)	50 [23, 108]	59 [24, 94]	44 [22, 177]
BM blasts (%)	36.5 [21.5, 58.0]	50.0 [36.5, 71.5]	30.3 [17.8, 39.5]
Peripheral blood blasts (%)	13.0 [3.0, 32.0]	22.0 [11.0, 60.0]	6.0 [1.0, 19.8]
IADL score			
8	18 (38.3)	7 (30.4)	11 (45.8)
6–7	16 (34.0)	9 (39.1)	7 (29.2)
⩽5	13 (27.7)	7 (30.4)	6 (25.0)
ECOG performance status			
0–1	33 (70.2)	16 (69.6)	17 (70.8)
2–4	14 (29.8)	7 (30.4)	7 (29.2)
CCI score ⩾3	5 (10.6)	4 (17.4)	1 (4.2)
Cytogenetic risk			
Favorable	4 (8.5)	4 (17.4)	0
Intermediate	26 (55.3)	11 (47.8)	15 (62.5)
Poor	17 (36.2)	8 (34.8)	9 (37.5)
FAB subtype			
M1	1 (2.1)	1 (4.3)	0
M2	27 (57.4)	9 (39.1)	18 (75.0)
M4	12 (25.5)	6 (26.1)	6 (25.0)
M5	4 (8.5)	4 (17.4)	0
M6	3 (6.4)	3 (13.0)	0
Serum albumin <34 g/L	13 (27.7)	7 (30.4)	6 (25.0)
IACA			
Unfit	31 (66.0)	16 (69.6)	15 (62.5)
Frail	16 (34.0)	7 (30.4)	9 (37.5)

Continuous variables are listed as median [interquartile range] and categorical variables as *n* (%).
AML, acute myeloid leukemia; BM, bone marrow; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; FAB, The French-American- British group; IACA, IADL, age, comorbidities, and albumin; IADL, instrumental activities of daily living; MDS, myelodysplastic syndrome.

Table 2. Responses and outcomes of molecular and cytogenetic abnormalities.

Genomic abnormality	Total	AML without MDS history	AML with MDS history	CR *n* (%)	Median OS (months)	1-year OS%
ASXL1	9	6	3	1 (11.1)	6.5	33.3
TET2	7	3	4	1 (14.3)	6.0	14.3
NPM1	7	6	1	1 (14.3)	9.3	14.3
DNMT3A	6	2	4	1 (16.7)	9.9	33.3
FLT3	6	4	2	0	9.6	16.7
TP53	6	5	1	0	5.5	0
RUNX1	4	2	2	0	11.8	50.0
IDH1/IDH2	3	2	1	0	9.9	33.3
EVI1	3	1	2	1 (33.3)	14.6	66.6
Complex karyotype	7	4	3	1 (14.3)	5.8	14.3
Monomeric karyotype	6	3	3	2 (33.3)	5.2	16.7

AML, acute myeloid leukemia; CR, complete remission; MDS, myelodysplastic syndrome; OS, overall survival.

significant difference was also observed between the intermediate and favorable cytogenetic risk groups and the poor cytogenetic risk group ($p = 0.261$) (Figure 2(c)). The median OS of patients with complex karyotype and monomeric karyotype was 5.8 and 5.2 months, respectively. The 1-year OS rates of the patients with complex karyotype and monomeric karyotype were 14.3% and 16.7%, respectively.

Regarding molecular abnormalities, the shortest OS was observed in patients with *TP53* mutations (median, 5.5 months; 1-year OS, 0%). Longer OS was observed among patients with *EVI1* mutations (median, 14.6 months; 1-year OS, 66.6%), *RUNX1* (median, 11.8 months; 1-year OS, 50.0%), and *DNMT3A* (median, 9.9 months; 1-year OS, 33.3%) (Table 2).

To better delineate the outcomes in the IACA subsets within our cohort, we analyzed cohorts of patients who were unfit and frail (Table 4). The median OS of these two groups was 11.2 (95% CI, 4.7−17.7) months in the unfit group and 6.0 (95% CI, 3.7−8.3) months in the frail group ($p = 0.005$). The 1-year OS rates were 49.2% and 23.4%, respectively. The 2-year OS rates were 21.6% and 0%, respectively (Figure 2(d)).

The most common reason for discontinuation of the trial during follow-up for survival was death in 38 of 47 (80.9%) patients [20 patients (87.0%) in the *de novo* AML group and 18 patients (75.0%) in the secondary AML group with a history of MDS]. Death was related to disease progression in 23 (48.9%) patients [13 (56.5%) in the *de novo* AML group and 10 (41.7%) patients in the secondary AML group].

Toxicities

No early mortality was observed in this study cohort. The 30-day mortality rate was zero. Table 5 summarizes grade ⩾3 AEs. Infectious AEs were the most common non-hematological toxicities (66.0%). Only three (6.4%) patients died of TRM (one in the AML without MDS history group and two in the AML with MDS history group). TRM was caused by infection ($n = 2$) or cerebral hemorrhage ($n = 1$). In the 47 patients who received low-dose decitabine therapy after diagnosis, the rates of TRM were lower than those who received chemotherapy or standard-dose decitabine, as reported previously. Overall, 38 deaths occurred in the study population. The causes of death were TRM ($n = 3$), PD ($n = 23$), infection ($n = 6$), hemorrhagic shock ($n = 1$),

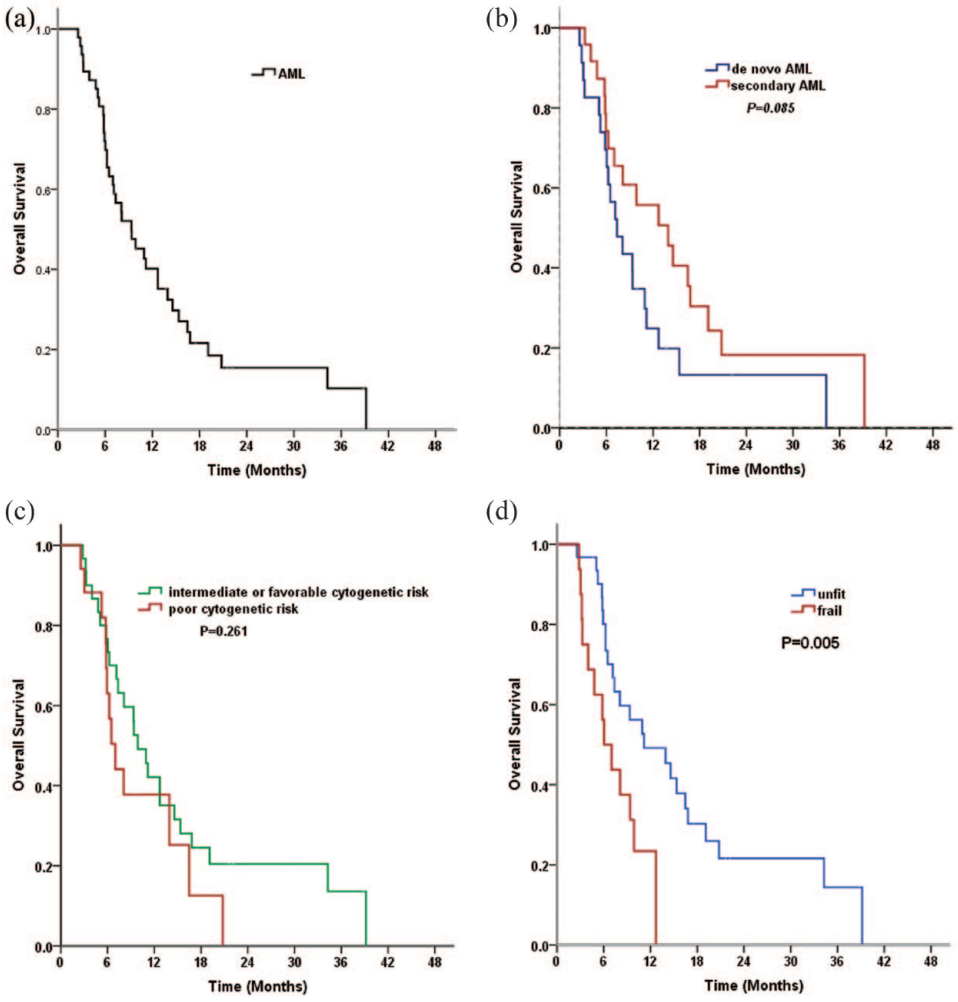

Figure 2. Overall survival. (a) Overall survival for the entire cohort, (b) overall survival of *de novo* AML or secondary AML, (c) overall survival of AML with intermediate/favorable cytogenetic risk or poor cytogenetic risk, and (d) overall survival of AML with IACA scores unfit *versus* frail. The distributions were estimated with the use of the Kaplan–Meier method and were compared with the log-rank test stratified according to AML types (*de novo* AML or secondary AML) and cytogenetic risk (intermediate/favorable risk or poor risk). The hazard ratio for death was estimated with the use of the Cox proportional-hazards model with the same stratification factors used in the log-rank test.
AML, acute myeloid leukemia; IACA, IADL, age, comorbidities, and albumin.

cerebral hemorrhage ($n=1$), heart failure ($n=1$), myocardial infarction ($n=2$), and acute kidney injury ($n=1$).

Discussion

Herein, we report a prospective single-arm clinical trial in previously untreated elderly patients with AML who were assessed as unfit for intensive chemotherapy using the IACA CGA and treated with low-dose decitabine. The CR + CRi and PR rates were 31.9% and 23.4%, respectively. Clinical benefit rate, median CR, and median OS in our study cohort were 61.7%, 8.9 and 9.4 months, respectively. The median OS was 11.2 months in the unfit group and 6.0 months in the frail group. The most common reason for discontinuing decitabine during follow-up was disease progression-related death. Only 3 (6.4%) patients died from TRM.

In a previous study, we observed that the IACA could predict clinical outcomes in elderly patients with AML.[5] In this study, we assessed older patients with AML using the IACA index. Untreated patients with AML who were

Table 3. Treatment outcomes of low-dose decitabine.

Characteristic	Total ($n=47$)	AML without MDS history ($N=23$)	AML with MDS history ($N=24$)	p Value
CR + CRi	15 (31.9)	4 (17.4)	11 (45.8)	**0.037**
PR	11 (23.4)	6 (26.1)	5 (20.8)	0.467
HI without an objective response	3 (6.4)	1 (4.3)	2 (8.3)	0.484
Treatment failure	18 (38.3)	12 (52.2)	6 (25)	0.096
Clinical benefit rate (CR + CRi + PR + HI only)	29 (61.7)	11 (43.5)	18 (75)	0.096
OS median (95% CI) months	9.4 (5.9, 12.8)	7.4 (4.9, 9.8)	13.9 (7.4, 20.5)	0.253
1-year OS (%)	36.1	19.9	45.7	0.053
2-year OS (%)	15.9	0	18.2	0.187
Early mortality ⩽30 days	0	0	0	–

AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; HI, hematologic improvement; MDS, myelodysplastic syndrome; OS, overall survival; PR, partial remission.
The bold font is used to highlight the values with statistical differences, i.e. data with $p<0.05$.

Table 4. Treatment outcomes of low-dose decitabine according to IACA score.

Characteristic	Total ($n=47$)	Unfit group ($N=31$)	Frail group ($N=16$)	p Value
CR or CRi	15 (31.9)	12 (38.7)	3 (18.8)	0.164
PR	11 (23.4)	6 (19.4)	5 (31.3)	0.853
HI without an objective response	3 (6.4)	2 (6.5)	1 (6.3)	0.979
Treatment failure	18 (38.3)	11 (35.5)	7 (43.8)	0.252
Clinical benefit rate (CR + CRi + PR + HI only)	29 (61.7)	20 (64.5)	9 (56.3)	0.252
OS median (95% CI) months	9.4 (5.9, 12.8)	11.2 (4.7, 17.7)	6.0 (3.7, 8.3)	**0.005**
1-year OS (%)	36.1	49.2	23.4	**0.015**
2-year OS (%)	15.9	21.6	0	0.111
Early mortality ⩽30 days	0	0	0	–

AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; HI, hematologic improvement; IACA, IADL, age, comorbidities, and albumin; MDS, myelodysplastic syndrome; OS, overall survival; PR, partial remission.
The bold font is used to highlight the values with statistical differences, i.e. data with $p<0.05$.

considered unfit or frail were included in our study. Garric *et al.*[34] have reported that CGA significantly affects hematological treatment decisions in older patients. Functional and mobility impairments, comorbidities, and age are predictive factors for changes in the treatment plan.[35] In our study, we compared the response to treatment and survival rates between the unfit and frail groups treated with low-dose decitabine. The median survival of the unfit group was longer than that of the frail group ($p=0.005$). The unfit group demonstrated a higher 1-year OS rate than the frail group ($p=0.015$). As for the 2-year OS rate, no

Table 5. Adverse events.

Events	*N* (%)
Treatment cycles median (range)	4 (1, 10)
Hematological AEs ⩾ grade 3	41 (87.2)
Anemia	30 (63.8)
Thrombocytopenia	34 (72.3)
Leukocytopenia	40 (85.1)
Neutropenia	40 (85.1)
Non-hematological AEs ⩾ grade 3	33 (70.2)
Neurologic adverse events	2 (4.3)
Gastrointestinal AEs	5 (10.6)
Infections	31 (66.0)
Cardiovascular adverse events	6 (12.8)
Discontinuation of treatment before six cycles decitabine	27 (57.4)
Causes of discontinuation of decitabine	
Disease progression	16 (34.0)
Treatment-related AEs	3 (6.4)
Cardiovascular events	3 (6.4)
Infections	4 (8.5)
Others	1 (2.1)

AEs, adverse events; PD, progressive disease; TRM, treatment-related mortality.

significant difference was observed between the two groups ($p = 0.111$).

HMAs are potentially active therapeutic alternatives with improved tolerability compared to intensive chemotherapy for AML.[15,36,37] Decitabine achieved a response rate of 26% in a multicenter trial in older patients with AML who were unfit for standard chemotherapy.[15,38] Currently, no optimal decitabine-dosing regimen is recommended. Decitabine has been studied in AML at various doses and schedules.[12,39] Blum *et al.*[40] have reported a CR rate of 47%, of which 64% achieved a morphologic leukemia-free state with a decitabine dose of 20 mg/m^2 administered for 10 consecutive days. Short *et al.*[23] have reported that the response rate with a 5-day decitabine regimen was 44%, whereas that with a 10-day schedule of decitabine was 40%. The median number of cycles received was two in the 5-day decitabine arm and three in the 10-day arm. Low-dose decitabine has been used in several studies to treat AML or MDS.[41–45] Low dose has no specific definition except that it ranges from 6 to 20 mg/m^2 for various durations. A pilot study of low-dose decitabine (6 mg/m^2/day for 10 days) treatment in elderly patients was conducted at our center. Five patients had received 6 mg/m^2/day decitabine for 10 days and were followed up for ⩾12 months. The survival times of these five patients were 18, 13, 7, 6, and 5 months, respectively, and the 1-year OS was 40%. Safety and efficacy were initially validated, and the treatment scheme was applied to the final project. In our study, 6 mg/m^2 decitabine administered for 10 days demonstrated good tolerability and adequate efficacy. The median number of completed decitabine cycles was four in our study, which was higher than the median number of cycles reported previously. The CR + CRi rate was 31.9%, and the clinical benefit rate was 61.7%.

It has been reported that almost half of patients with AML are >70 years of age at the time of diagnosis and frequently have significant comorbidities and poor performance status; many are considered unfit for intensive chemotherapy.[1] The use of HMAs, such as decitabine, as induction therapy has become a commonly used strategy for older adults with AML. Several combinatorial approaches have been investigated to improve the outcome of single-agent HMAs.[46–48] The oral Bcl-2 inhibitor, venetoclax, with azacitidine is emerging as a new standard therapeutic strategy for older patients with AML. However, the high price of venetoclax, not covered by medical insurance in China, has limited its widespread application. Combining venetoclax with azacitidine resulted in promising CR/CRi rates of 66% in older patients with AML, with a median OS of 17.5 months.[18] Our study is of significant relevance for determining the best dose and duration of decitabine therapy for older patients with AML who are considered unfit or frail for induction chemotherapy. Approximately 70% of our patients were aged >75 years. Treatment with low-dose decitabine for 10 days suggests equivalent efficacy and better tolerance than those with standard-dose decitabine in a situation where venetoclax could not be obtained previously in China. These results have implications for combination therapy in older patients with frailty.

In our study, as in most studies on AML treatment, the responders lived significantly longer than the non-responders. The median OS of the patients treated with low-dose decitabine in our study was similar to that reported in clinical trials, single-center studies, and previous population-based studies. The median OS (9.4 months) was not significantly different from that reported in the DACO-016 trial (7.7 months).[14] A meta-analysis of newly diagnosed patients with AML aged ⩾60 years treated with decitabine reported a pooled median OS of 8.1 months.[3] The median number of cycles of low-dose decitabine in our study was 4 (range, 1–10). The TRM rate in this study was only 6.4%. Hence, low-dose decitabine in a 10-day schedule may yield a survival benefit, tolerability, and an economical dosing scheme.

Among patients with or without a history of MDS, the CR plus CRi rate was higher in patients with AML and a history of MDS, which could be ascribed to increased methylation abnormalities in patients with AML and a history of MDS. However, the advantage in CR rate did not lead to a difference in OS, suggesting the need for a better scheme to maintain efficacy.

This study had several limitations. This was a single-arm study with a small sample size and lacked an active control group. The small sample size limits the statistical analyses. To minimize the impact of selection bias in the final analysis, we conducted this prospective study according to strict established inclusion and exclusion criteria. Designated assessors were assigned to conduct the IACA assessment of the patients included in our study. All eligible patients who met the inclusion criteria and voluntarily signed an informed consent form were screened for inclusion. All enrolled patients were treated in strictly accordance with the study protocol. The prolonged time from diagnosis to treatment initiation suggests that the patients included in this study had relatively indolent disease biology. High-quality studies are urgently needed to identify the best decitabine administration scheme for older patients with AML unsuitable for standard induction therapy. Azacitidine is commonly used in older patients with AML unfit for chemotherapy and has been demonstrated to improve outcomes.[13] Labrador *et al.*[48] have reported no significant differences in the response and OS rates in patients with AML treated with azacitidine or decitabine. However, the more effective hypomethylation drug remains undetermined. We did not compare these two hypomethylation drugs and could not conclude which is better.

Conclusion

This prospective study demonstrated the efficacy and acceptable safety profile of low-dose decitabine as a single agent in older, untreated patients with AML who were unfit for induction therapy in China. The application of the IACA index in elderly patients with AML to screen those unsuitable for standard chemotherapy makes the selection of treatment strategies for elderly patients with AML more objective. Our study provides a new, safe, and tolerable treatment scheme for elderly patients with AML. Further randomized studies are needed to confirm this finding.

Declarations

Ethics approval and consent to participate

This trial was registered on www.chictr.org.cn as ChiCTR1800018853. The study protocol was reviewed and approved by the institutional review boards of all participating institutions. Written informed consent for treatment administration and data collection was provided by all patients before any study-related procedures commenced. This study was conducted following the principles of the Declaration of Helsinki and the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice.

Consent for publication

Informed consent for publication from all participants were obtained and the details from the participants were de-identified.

Author contributions

Ru Feng: Conceptualization; Investigation; Software; Writing – original draft.

Shuai Zhang: Data curation; Methodology.

Jiang-Tao Li: Investigation; Project administration.

Ting Wang: Data curation; Project administration.

Chun-Li Zhang: Investigation; Project administration.

Jie-Fei Bai: Data curation; Project administration.

Lei Yang: Formal analysis; Project administration.

Li-Ru Wang: Data curation; Project administration.

Hong-Mei Jing: Data curation; Project administration; Validation.

Hui Liu: Conceptualization; Methodology; Resources; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
All data used in the analysis were anonymized, making it impossible for researchers to identify individuals.

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Supplemental material
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